(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 512 570 A1**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92107863.0**

(22) Date of filing: **11.05.92**

(51) Int. Cl.^{5}: **C07D 333/58**, C07D 307/81, C07D 209/14, C07D 407/12, C07D 405/12, C07D 409/12, A61K 31/44, A61K 31/40, A61K 31/38, A61K 31/335

(30) Priority: **10.05.91 GB 9110133**
14.06.91 GB 9112823
23.12.91 GB 9127277

(43) Date of publication of application: **11.11.92 Bulletin 92/46**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU NL PT SE**

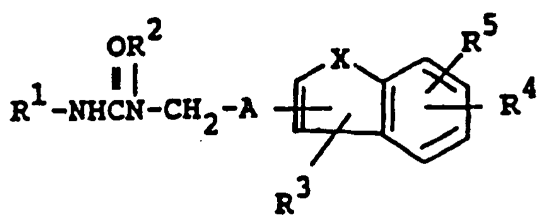
(71) Applicant: **FUJISAWA PHARMACEUTICAL CO., LTD.**
4-7, Doshomachi 3-chome Chuo-ku
Osaka-shi Osaka 541(JP)

(72) Inventor: **Yoshikuni, Itoh**
4-16-4-305, Azuma, Tsukuba-shi
Ibaraki 305(JP)
Inventor: **Kazuhiko, Ohne**
2-25-10, Matsushiro, Tsukuba-shi
Ibaraki 305(JP)
Inventor: **Hirokazu, Tanaka**
1-4-8, Ottominami, Tsuchiura-shi
Ibaraki 300(JP)

(74) Representative: **Türk, Dietmar, Dr. rer. nat.**
Türk, Gille, Hrabal, Leifert Patentanwälte
Brucknerstrasse 20
W-4000 Düsseldorf 13(DE)

(54) **Urea derivatives, processes for the preparation thereof and pharmaceutical composition comprising the same.**

(57) A compound of the formula :



. (I)

wherein

R^1 is aryl which may be substituted with halogen, nitro, amino, lower alkylamino, lower alkoxy or acylamino,

R^2 is hydrogen; alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, cyclo(lower)-alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy;

R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,

R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,

R^5 is hydrogen, halogen, lower alkyl or aryl,

EP 0 512 570 A1

A is a single bond or lower alkylene, and
X is O, S or NH,
provided that
R^3 is aryl which may be substituted with halogen, nitro, amino or lower alkyamino, or
R^4 is halogen, lower alkoxy or aryl which may be substituted with halogen,
when
R^2 is cycloalkyl,

and pharmaceutically acceptable salts thereof, processes for their preparation and pharmaceutical compositions comprising them.

This invention relates to new urea derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new urea derivatives and pharmaceutically acceptable salts thereof which have an inhibitory activity against acyl-CoA : cholesterol acyltransferase enzyme (hereinafter, ACAT), to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

One object of this invention is to provide new and useful urea derivatives and pharmaceutically acceptable salts which possess an inhibitory activity against ACAT.

Another object of this invention is to provide processes for preparation of said urea derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said urea derivatives and pharmaceutically acceptable salts thereof.

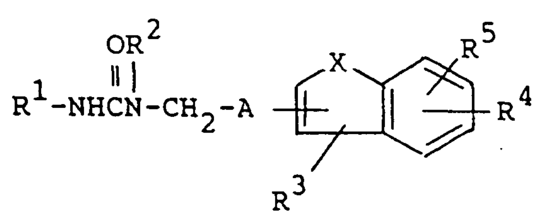
Still further object of this invention is to provide a therapeutic method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby in human beings or animals, using said urea derivatives and pharmaceutically acceptable salts thereof.

High levels of blood cholesterol and blood lipids are conditions which are involved in the onset of atherosclerosis.

It is well known that inhibition of ACAT-catalyzed cholesterol esterification could lead to diminish intestinal absorption of cholesterol as well as a decrease in the intracellular accumulation of cholesterol esters in the intima of the arterial wall. Therefore, ACAT inhibitors are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby such as cardiac insufficiency (e.g. angina pectoris, myocardial infarction, etc.), cerebrovascular disturbance (e.g. cerebral infarction, cerebral apoplexy, etc.), arterial aneurism, peripheral vascular disease, xanthomas, restenosis after percutaneous transluminal coronary angioplasty, or the like.

Some urea derivatives have been known as ACAT inhibitors, for example, in U.S. Patent Nos. 4,473,579 and 4,623,662, EP Patent Application Publication Nos. 0354994 and 0399422 and PCT Patent Application No. PCT/WO91/13871.

The object urea derivatives of this invention are new and can be represented by the following general formula (I) :



(I)

wherein

- R^1 is aryl which may be substituted with halogen, nitro, amino, lower alkylamino, lower alkoxy or acylamino,
- R^2 is hydrogen; alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, cyclo-(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy;
- R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,
- R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,
- R^5 is hydrogen, halogen, lower alkyl or aryl,
- A is a single bond or lower alkylene, and X is O, S or NH, provided that
- R^3 is aryl which may be substituted with halogen, nitro, amino or lower alkylamino, or
- R^4 is halogen, lower alkoxy or aryl which may be substituted with halogen,
  when
- R^2 is cycloalkyl,

and pharmaceutically acceptable salts thereof.

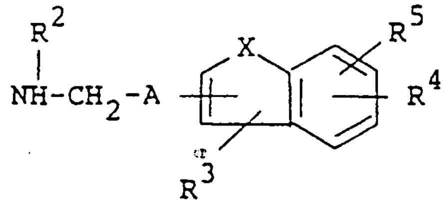
The object compound (I) or its salt can be prepared by processes as illustrated in the following reaction schemes.

Process 1

R^1-NCO

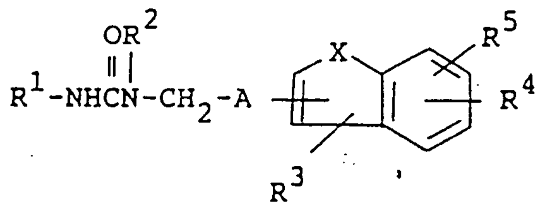
(II)

+



(III)
or its salt

$\longrightarrow$



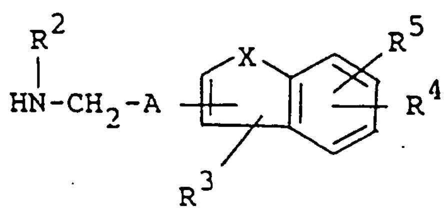
(I)
or its salt

Process 2

R^1-NH_2

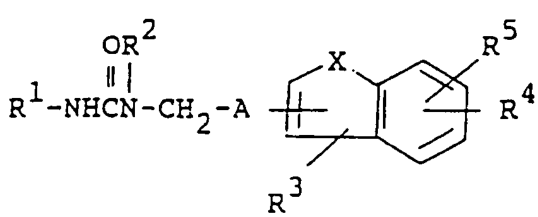
(IV)
or its salt

+



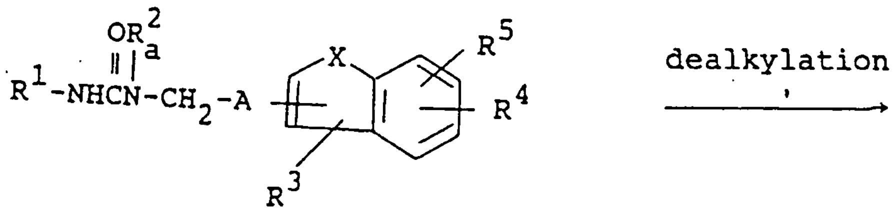
(III)
or its salt

formation of ureido group $\longrightarrow$

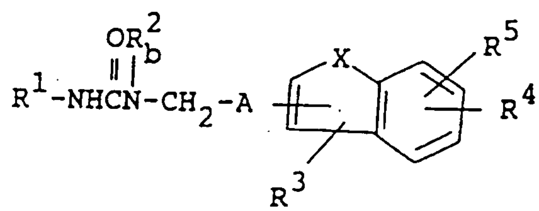


(I)
or its salt

Process 3

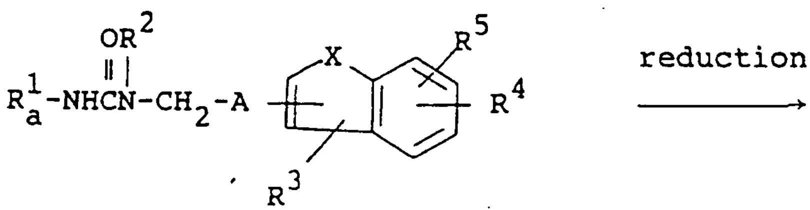


(Ia)
or its salt

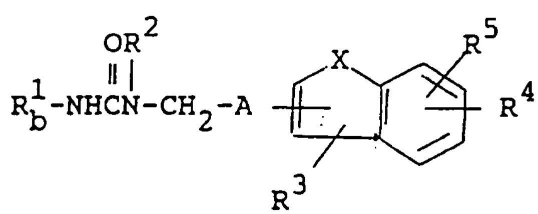


(Ib)
or its salt

Process 4

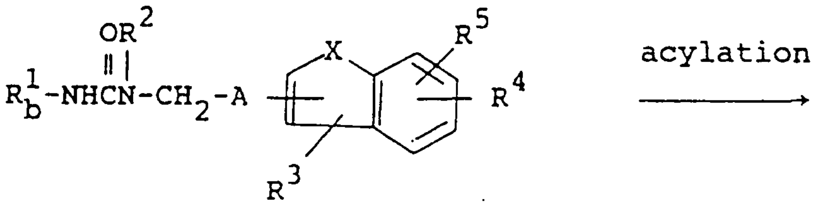


(Ic)
or its salt

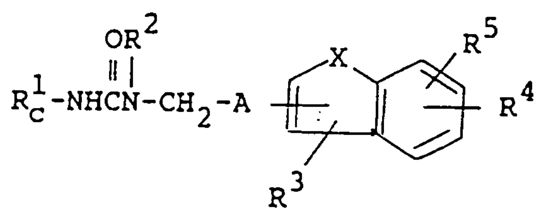


(Id)
or its salt

Process 5

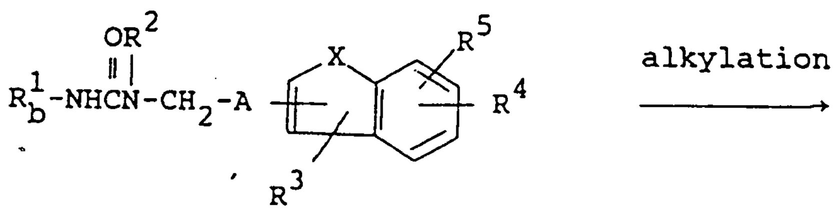


(Id)
or its salt

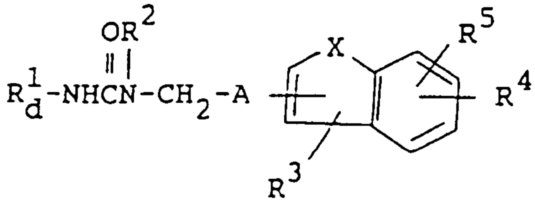


(Ie)
or its salt

Process 6



(Id)
or its salt



(If)
or its salt

wherein

R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,

R^2_a is lower alkyl which is substituted with aryl substituted with lower alkoxy,
R^2_b is lower alkyl which is substituted with aryl substituted with hydroxy,
R^1_a is aryl substituted with nitro,
R^1_b is aryl substituted with amino,
R^1_c is aryl substituted with acylamino, and
R^1_d is aryl substituted with lower alkylamino.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the term "cyclo(lower)alkyl" is intended to mean a group having 3 to 6 carbon atoms.

The lower moiety in the term "cyclo(lower)alkenyl" is intended to mean a group having 3 to 6 carbon atoms.

The term "alkyl" may include lower alkyl and higher alkyl.

The term "cycloalkyl" may include cyclo(lower)alkyl and cyclo(higher)alkyl.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkylamino" and "ar(lower)alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl or the like, in which preferable one is methyl, ethyl, propyl, isopropyl, pentyl or isopentyl.

Suitable "cyclo(lower)alkyl" may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Suitable "cyclo(lower)alkenyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise provided.

Suitable "higher alkyl" may be a straight or branched one such as heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, methylheptyl, methyloctyl, methylnonyl, methyldecyl, ethylheptyl, ethyloctyl, ethylnonyl, ethyldecyl or the like, in which preferable one is one having 7 to 10 carbon atoms and the most preferable one is heptyl or nonyl.

Suitable "cyclo(higher)alkyl" may be cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclotridecyl, cyclotetradecyl, cyclopentadecyl, cyclohexadecyl, cycloheptadecyl, cyclooctadecyl, cyclononadecyl, cycloeicosyl, in which preferable one is having 7 to 10 carbon atoms and the most preferable one is cycloheptyl.

Suitable "lower alkoxy" may be a straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy or the like, in which preferable one is methoxy.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine, in which preferable one is fluorine or chlorine.

Suitable "aryl" may be phenyl, naphthyl, phenyl substituted with lower alkyl (e.g. tolyl, xylyl, mesityl, cumenyl, diisopropylphenyl, etc.) and the like, in which preferable one is phenyl or phenyl substituted with lower alkyl.

Suitable "lower alkylamino" may be mono or di(lower alkyl)amino such as methylamino, ethylamino, dimethylamino, diethylamino or the like, in which preferable one is dimethylamino.

Suitable "ar(lower)alkyl" may be phenyl(lower)alkyl (e.g. benzyl, phenethyl, phenylpropyl, etc.), benzhydryl, trityl, tolylmethyl, xylylmethyl, mesitylmethyl, cumenylmethyl, and the like, in which preferable one is phenyl(lower)alkyl and the most preferable one is benzyl.

Suitable "lower alkylene" may be a straight or branched one such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, ethylethylene, or the like.

The aryl groups for R^1, R^3 and R^4 may be substituted with 1 to 5 substituent(s) as mentioned above, wherein the preferable number of the substituent(s) is 1, 2 or 3.

The aryl group as substituent of lower alkyl for R^2 may be substituted with 1 to 5 substituent(s) as stated above, wherein the preferable number of the substituent(s) is 1, 2 or 3.

Preferable "aryl substituted with halogen" is chlorophenyl, dichlorophenyl, difluorophenyl, trichlorophenyl or trifluorophenyl.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl,

pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

saturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, etc.;

unsaturated, condensed heterocyclic group containing 1 to 2 oxygen atom(s) for example, benzofuranyl, etc.;

or the like.

Preferable one in a heterocyclic group is pyridyl or furyl.

Suitable acyl moiety in the term "acylamino" may be carboxy; esterified carboxy; carbamoyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl, cyclo(lower)alkyl, aryl and hydroxy; lower alkanoyl; a heterocycliccarbonyl; lower alkylsulfonyl; and the like.

The esterified carboxy may be substituted or unsubstituted lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, etc.], substituted or unsubstituted aryloxycarbonyl [e.g. phenoxycarbonyl, 4-nitrophenoxycarbonyl, 2-naphthyloxycarbonyl, etc.], substituted or unsubstituted ar(lower)alkoxycarbonyl [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, 4-nitrobenzyloxycarbonyl, etc.] and the like.

The lower alkanoyl may be formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and the like, in which preferable one is acetyl.

The heterocyclic moiety in the term "heterocycliccarbonyl" may be the same as those exemplified for "heterocyclic group".

The lower alkylsulfonyl may be methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like, in which the preferable one is methylsulfonyl.

Suitable "acylamino" may be lower alkanoylamino and lower alkylsulfonylamino, in which preferable one is acetylamino or methylsulfonylamino.

Preferable compound (I) is one which has aryl (more preferably phenyl or phenyl substituted with lower alkyl) optionally substituted with halogen, nitro, amino, lower alkylamino, lower alkoxy, lower alkanoylamino or lower alkylsulfonylamino for R^1, hydrogen; alkyl; cycloalkyl; or lower alkyl substituted with cyclo(lower)-alkyl, cyclo(lower)alkenyl, a heterocyclic group (more preferably pyridyl or furyl) or aryl (more preferably phenyl or phenyl substituted with lower alkyl) optionally substituted with halogen, hydroxy or lower alkoxy for R^2, hydrogen, lower alkyl or aryl (more preferably phenyl or phenyl substituted with lower alkyl) optionally substituted with halogen for R^3, hydrogen, halogen, lower alkyl or aryl (more preferably phenyl) for R^4, hydrogen or lower alkyl for R^5, a single bond or lower alkylene for A, and O or S for X; or aryl (more preferably phenyl or phenyl substituted with lower alkyl) optionally substituted with halogen, nitro, amino, lower alkylamino or lower alkoxy for R1, alkyl, cycloalkyl or ar(lower)alkyl [more preferably phenyl(lower)-alkyl] for R^2, hydrogen, lower alkyl or aryl (more preferably phenyl) optionally substituted with halogen, nitro, amino or lower alkylamino for R^3, hydrogen, halogen, lower alkyl, lower alkoxy or aryl (more preferably phenyl) optionally substituted with halogen for R^4, hydrogen for R^5, a single bond or lower alkylene for A, and O or S for X.

More preferable compound (I) is one which has aryl (more preferably phenyl) substituted with halogen for R^1, alkyl or ar(lower)alkyl (more preferably phenyl(lower)alkyl) for R^2, aryl (more preferably phenyl) substituted with halogen for R^3, lower alkyl for R^4, hydrogen for R^5, a single bond or lower alkylene for A,

and O for X.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an alkali metal salt [e.g. sodium salt, potassium salt, etc.] or the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or its salt can be prepared by reacting a compound (II) with a compound (III) or its salt.

Suitable salt of the compound (III) may include an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic base salt [e.g. sodium salt, potassium salt, etc.] or the like.

The reaction is usually carried out in a conventional solvent such as dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, or any other organic solvent which does not adversely influence the reaction.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is preferably carried out under cooling or at ambient temperature.

Process 2

The object compound (I) or its salt can be prepared by subjecting a compound (IV) or its salt and a compound (III) or its salt to formation reaction of ureido group.

Suitable salts of the compounds (III) and (IV) may be the same as those exemplified for the compound (I).

This reaction is carried out in the presence of reagent which introduces carbonyl group such as phosgene, haloformate compound [e.g. ethyl chloroformate, trichloromethyl chloroformate, etc.], N,N'-carbonyldiimidazole, metal carbonyl compounds [e.g. cobalt carbonyl, manganese carbonyl, etc.], a combination of carbon monoxide and catalysts such as palladium chloride, etc., or the like.

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, toluene, chloroform, methylene chloride, N,N-dimethylformamide, ethyl acetate or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 3

The object compound (Ib) or its salt can be prepared by subjecting a compound (Ia) or its salt to dealkylation reaction.

Suitable salts of the compounds (Ia) and (Ib) may be acid addition salts as exemplified for the compound (I).

The reaction is carried out in the presence of an acid including Lewis acid [e.g. hydrochloric acid, hydrobromic acid, hydroiodic acid, boron tribromide, boron trichloride, etc.] or tri(lower alkyl)silyliodide [e.g. trimethylsilyliodide, etc.].

The reaction is usually carried out in a solvent such as water, acetic acid, methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 4

The object compound (Id) or its salt can be prepared by subjecting a compound (Ic) or its salt to reduction.

Suitable salts of the compounds (Ic) and (Id) may be referred to the ones as exemplified for the compound (I).

The present reduction is carried out by chemical reduction, catalytic reduction, or the like.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent and other conventional solvent such as diethyl ether, methylene chloride, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

In this reaction, in case that the compound (Ic) having aryl substituted with nitro for R^3 is used as a starting compound, the compound (Id) having aryl substituted with amino for R^3 may be obtained according to reaction conditions. This case is included within the scope of the present reaction.

Process 5

The object compound (Ie) or its salt can be prepared by reacting a compound (Id) or its salt with an acylating agent.

Suitable salt of the compound (Ie) may be the same as those exemplified for the compound (I).

The acylating agent may be include an organic acid represented by the formula : R^6-OH, in which R^6 is acyl as illustrated above, or its reactive derivative.

The suitable reactive derivative of organic acid may be a conventional one such as an acid halide [e.g. acid chloride, acid bromide, etc.], an acid azide, an acid anhydride, an activated amide, an activated ester or the like.

When free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide or the like.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, acetonitrile, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction is also preferably carried out in the presence of a conventional base such as triethylamine, pyridine, sodium hydroxide or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 6

The object compound (If) or its salt can be prepared by reacting a compound (Id) or its salt with an alkylating agent.

Suitable salts of the compound (If) may be the same as those exemplified for the compound (I).

Suitable alkylating agent may be lower alkyl halide [e.g. methyl iodide, ethyl bromide, etc.], a combination of a carbonyl compound such as aliphatic ketone [e.g. acetone, ethyl methyl ketone, etc.], carbaldehyde [e.g. formaldehyde, ethanal, etc.], orthocarboxylic acid ester [e.g. triethyl orthoformate, etc.] or the like, and a reducing agent including chemical and catalytic ones [e.g. formic acid, sodium borohydride, sodium cyanoborohydride, palladium on carbon, etc.].

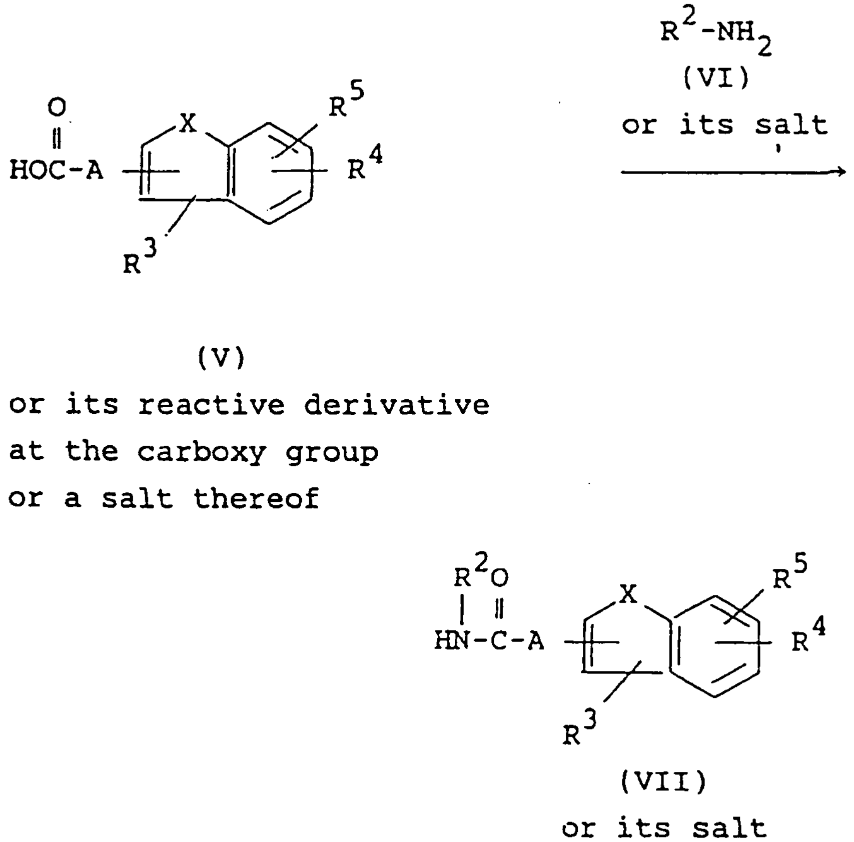
The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dioxane, an alcohol [e.g. methanol, ethanol, etc.], acetonitrile, tetrahydrofuran, N,N-dimethylformamie, or a mixture thereof. Additionally, in case that the above-mentioned alkylating agent are in liquid, they can also be used as a solvent.

The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

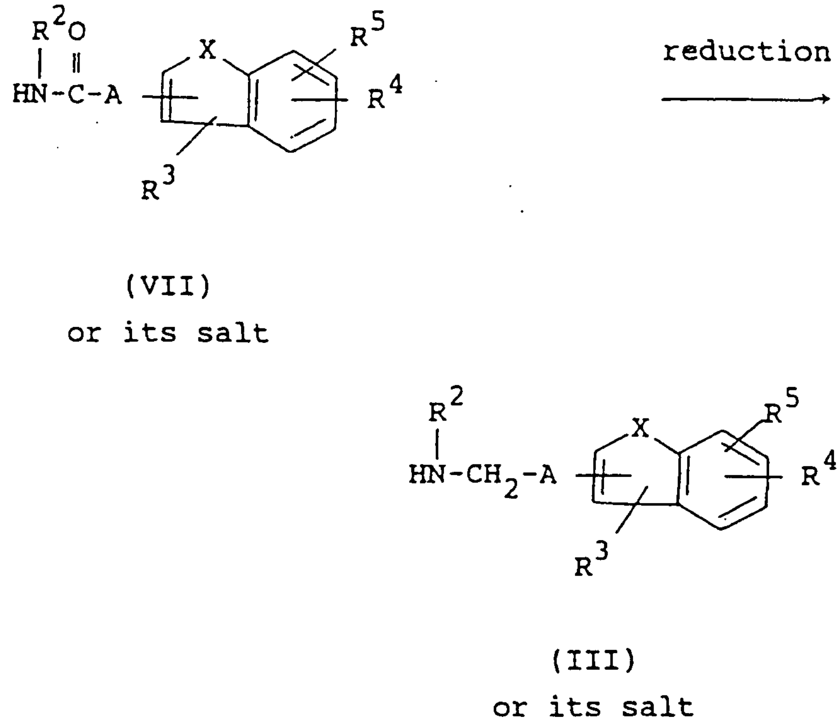
In this reaction, in case that the compound (Id) having aryl substituted with amino for R^3 is used as a starting compound, the compound (If) having aryl substituted with lower alkylamino may be obtained according to reaction conditions. This case is included within the scope of the present reaction.

Among the starting compound (III), some of them are new and can be prepared by processes as illustrated in the following reaction schemes.

Process A



Process B



wherein R^2, R^3, R^4, R^5, A and X are each as defined above.

The above-mentioned processes for preparing the starting compound are explained in detail in the following.

Process A

The compound (VII) or its salt can be prepared by reacting a compound (V) or its reactive derivative at the carboxy group or a salt thereof with a compound (VI) or its salt.

Suitable salts of the compounds (V), its reactive derivative and the compounds (VI) and (VII) may be the same as those exemplified for the compound (I).

Suitable reactive derivative of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g. methanesulfonic aid, etc.), alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2\ N^{+}=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with an N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, etc.) and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

The reaction is usually carried out in a conventional solvent such as water, an alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

When the compound (V) is used in free acid form or its salt form in the reaction, the reaction is

preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimthylaminopropyl)-carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical and the reaction can be carried out under cooling to heating.

Process B

The compound (III) or its salt can be prepared by reacting a compound (VII) or its salt with a reducing agent.

Suitable salt of the compound (VII) may be the same as those exemplified for the compound (I).

Suitable reducing agent may be diborane, metal hydride [e.g. lithium aluminum hydride, etc.], a combination of metal hydride [e.g. lithium aluminum hydride, etc.] and Lewis acid [e.g. aluminum chloride, etc.], and the like.

The reaction is usually carried out in a conventional solvent such as diethyl ether, tetrahydrofuran or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

The compounds obtained by the above process can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atom(s), and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity against ACAT, and are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test :

Acyl-CoA : cholesterol acyltransferase (ACAT) inhibitory activity

Method :

ACAT activity was measured by the method of Heider et al. described in Journal of Lipid Research, Vol. 24, page 1127 (1983). The enzyme ACAT was prepared from the mucosal microsome fraction of the small intestine of male, 18-week old Japanese white rabbits which had been fed diet containing 2% cholesterol for 8 weeks. The inhibitory activity of compounds were calculated by measuring the amount of the labeled cholesterol ester produced from [^{14}C]oleoyl-CoA and endogenous cholesterol as follows. [^{14}C]oleoyl-CoA and microsome were incubated with test compounds at 37°C for 5 minutes. The reaction was stopped by the addition of chloroform-methanol (2:1, V/V). Cholesterol ester fraction in the chloroform-methanol extracts was isolated by thin-layer chromatography and was counted their label.

Results

Test Compound (Example No.)	IC50 (M)
3 - (9)	7.3 x 10-8
3 - (10)	2.4 x 10-8
3 - (35)	6.6 x 10-9
5 - (7)	8.8 x 10-9
5 - (15)	8.9 x 10-9
6 - (2)	7.4 x 10-9
6 - (6)	8.4 x 10-9
6 - (7)	4.4 x 10-9

For therapeutic purpose, the compound (I) of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

A mixture of 3-phenyl-2-benzofurancarboxylic acid (1 g) and thionyl chloride (2 ml) was stirred at 80°C for 30 minutes. After cooling excess thionyl chloride was removed under the reduced pressure, and then thionyl chloride was removed with benzene azeotropically to give 3-phenyl-2-benzofurancarbonyl chloride (1.08 g). To a stirred solution of 1-heptylamine (0.5 g) and triethylamine (0.8 ml) in methylene chloride (25 ml) was added a solution of 3-phenyl-2-benzofurancarbonyl chloride (1.08 g) in methylene chloride (5 ml) dropwise at 0°C and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was washed with 1N aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and water, and dried. Evaporation of solvent gave the residue which was purified by column chromatography.
Elution with chloroform gave
N-heptyl-3-phenyl-2-benzofurancarboxamide (1.58 g).
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.30 (8H, m), 1.55 (2H, m), 3.40 (2H, q, J=7Hz), 6.53 (1H, t, J=7Hz), 7.31-7.68 (9H, m)

Preparation 2

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) N-Heptyl-3-phenyl-2-benzo[b]thiophenecarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.13-1.26 (10H, m), 3.21 (2H, q, J=7Hz), 5.56 (1H, t, J=7Hz), 7.32-7.61 (8H, m), 7.90 (1H, dd, J=2, 8Hz)

(2) N-Heptyl-5-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.32-1.40 (8H, m), 1.67 (2H, m), 3.51 (2H, q, J=7Hz), 6.65 (1H, t, J=7Hz), 7.32-7.68 (8H, m), 7.86 (1H, d, J=2Hz)

(3) N-Heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.62-1.70 (2H, m), 3.49 (2H, q, J=7Hz), 6.64 (1H, br s), 7.27-7.54 (6H, m), 7.69 (1H, d, J=8Hz)

(4) N-Cycloheptyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.55 (10H, br s), 1.95-2.07 (2H, m), 4.12 (1H, br s), 6.48 (1H, d, J=9Hz), 7.25-7.69 (9H, m)

(5) 3-(4-Chlorophenyl)-N-heptyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.55-1.65 (2H, m), 2.44 (3H, s), 3.43 (2H, q, J=7Hz), 6.62 (1H, br t, J=7Hz), 7.28-7.63 (7H, m)
(6) N-Heptyl-5-isopropyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (6H, d, J=7Hz), 1.32 (8H, s), 1.53-1.60 (2H, m), 3.00 (1H, sep, J=7Hz), 3.40 (2H, q, J=7Hz), 6.50 (1H, br s), 7.30-7.69 (8H, m)
(7) 3,5-Diphenyl-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, br s), 1.50-1.62 (2H, m), 3.42 (2H, q, J=7Hz), 6.53 (1H, br s), 7.33-7.75 (13H, m)
(8) 3-(2-Chlorophenyl)-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.30 (8H, br s), 1.50-1.61 (2H, m), 3.40 (2H, q, J=7Hz), 6.51 (1H, br t, J=7Hz), 7.23-7.58 (8H, m)
(9) 3-(4-Chlorophenyl)-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.33 (8H, br s), 1.55-1.65 (2H, m), 3.43 (2H, q, J=7Hz), 6.65 (1H, br t, J=7Hz), 7.30-7.64 (8H, m)
(10) N-Heptyl-3-(2-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.23 (8H, br s), 1.39-1.52 (2H, m), 2.19 (3H, s), 3.34 (2H, q, J=7Hz), 6.20 (1H, br t, J=7Hz), 7.21-7.63 (8H, m)
(11) N-Heptyl-3-(3-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.50-1.60 (2H, m), 2.45 (3H, s), 3.40 (2H, q, J=7Hz), 6.46 (1H, br t, J=7Hz), 7.28-7.60 (8H, m)
(12) N-Heptyl-5-methyl-3-(4-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (8H, m), 1.54 (2H, m), 2.41 (3H, s), 2.42 (3H, s), 3.38 (2H, q, J=7Hz), 6.48 (1H, br t, J=7Hz), 7.22-7.54 (7H, m)
(13) N-Heptyl-3-(4-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.30 (8H, m), 1.55 (2H, m), 2.42 (3H, s), 3.40 (2H, q, J=7Hz), 6.51 (1H, br t, J=7Hz), 7.29-7.62 (8H, m)
(14) N-Heptyl-5-isopentyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 0.94 (6H, d, J=7Hz), 1.29-1.36 (8H, m), 1.50-1.68 (5H, m), 2.71 (2H, t, J=7Hz), 3.47 (2H, q, J=7Hz), 6.62 (1H, br t, J=7Hz), 7.23 (1H, dd, J=2, 8Hz), 7.37-7.45 (3H, m)
(15) N-Benzyl-3-(4-chlorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 4.61 (2H, d, J=5.5Hz), 6.92 (1H, br t, J=5.5Hz), 7.23-7.40 (8H, m), 7.45 (2H, d, J=8Hz), 7.61 (2H, d, J=8Hz)
(16) 3-(4-Chlorophenyl)-N-cycloheptyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.62 (10H, br s), 1.97-2.08 (2H, m), 2.43 (3H, s), 4.05-4.18 (1H, m), 6.58 (1H, d, J=8Hz), 7.23-7.61 (7H, m)
(17) 3-(4-Chlorophenyl)-5-methyl-N-pentyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.35 (4H, br s), 1.54-1.68 (2H, m), 2.44 (3H, s), 3.42 (2H, q, J=7Hz), 6.63 (1H, br t, J=7Hz), 7.25-7.35 (2H, m), 7.40-7.50 (3H, m), 7.61 (2H, dd, J=9, 2Hz)
(18) 3-(4-Chlorophenyl)-5-methyl-N-nonyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (12H, br s), 1.55-1.65 (2H, m), 2.43 (3H, s), 3.40 (2H, q, J=7Hz), 6.62 (1H, br t, J=7Hz), 7.23-7.63 (7H, m)
(19) 3-(4-Chlorophenyl)-5,7-dimethyl-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 1.32 (8H, br s), 1.58-1.67 (2H, m), 2.39 (3H, s), 2.55 (3H, s), 3.43 (2H, q, J=7Hz), 6.63 (1H, br t, J=7Hz), 7.09 (1H, s), 7.18 (1H, s), 7.45 (2H, d, J=7Hz), 7.60 (2H, d, J=7Hz)
(20) 5-Chloro-N-heptyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.28 (8H, br s), 1.55 (2H, m), 3.39 (2H, dt, J=5, 7Hz), 6.49 (1H, t, J=5Hz), 7.37-7.63 (8H, m)
(21) N-Heptyl-5-methyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.28 (8H, br s), 1.52-1.65 (2H, m), 2.44 (3H, s), 3.40 (2H, q, J=7Hz), 6.50 (1H, br s), 7.22-7.68 (8H, m)

Preparation 3

To a suspension of lithium aluminum hydride (0.32 g) in tetrahydrofuran (20 ml) was added aluminum chloride (0.37 g) in some portions at 0°C with stirring, and the mixture was stirred at 0°C for 15 minutes. To this mixture was added a solution of N-heptyl-3-phenyl-2-benzo[b]thiophenecarboxamide (2.9 g) in

tetrahydrofuran (10 ml) dropwise at 0°C and the mixture was stirred for 3 hours under reflux. After cooling excess aluminum hydride was destroyed with diethyl ether saturated with water. Inorganic material was filtered off. Solvent was evaporated to leave the residue which was taken up in diethyl ether. The organic solution was washed with 1N aqueous sodium hydroxide, dried and evaporated to afford N-heptyl-(3-phenylbenzo[b]thiophen-2-ylmethyl)amine (2.63 g) as an oil.
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.24 (8H, s), 1.44 (2H, m), 2.59 (2H, t, J=7Hz), 4.02 (2H, s), 7.28-7.86 (9H, m)

Preparation 4

A mixture of 4'-chloro-2-hydroxy-5-methylbenzophenone (2.8 g), ethyl bromoacetate (2.1 g) and potassium carbonate (3.5 g) in acetone (30 ml) was stirred for 4 hours under reflux. After cooling potassium carbonate was filtered off. Evaporation of solvent gave the residue which was dissolved in chloroform. The chloroform solution was washed with water and dried. Evaporation of solvent gave the residue which was recrystallized from ethanol to afford ethyl [2-(4-chlorobenzoyl)-4-methylphenoxy]acetate (3.5 g).
NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 2.32 (3H, s), 4.16 (2H, q, J=7Hz), 4.49 (2H, s), 6.73 (1H, d, J=8Hz), 7.25 (2H, d, J=8Hz), 7.40 (2H, d, J=8Hz), 7.81 (2H, d, J=8Hz)

Preparation 5

A mixture of ethyl [2-(4-chlorobenzoyl)-4-methylphenoxy]acetate (3.0 g) and sodium ethoxide (0.64 g) in ethanol (30 ml) was refluxed for 1 hour. To this mixture was added 1N aqueous sodium hydroxide (12 ml) at ambient temperature and the mixture was refluxed for 30 minutes. After cooling ethanol was evaporated to give a residue which was acidified with concentrated hydrochloric acid (6 ml). The resulting crystal was collected by filtration and washed with water. Recrystallization from ethanol gave 3-(4-chlorophenyl)-5-methyl-2-benzofurancarboxylic acid (1.27 g).
NMR ($CDCl_3$, δ) : 7.58-7.30 (7H, m), 2.45 (3H, s)

Preparation 6

To a suspension of lithium aluminum hydride (0.57 g) in tetrahydrofuran (30 ml) was added aluminum chloride (0.67 g) in some portions at 0°C with stirring, and the mixture was stirred at 0°C for 15 minutes. To this mixture was added a solution of 3-(4-chlorophenyl)-N-heptyl-5-methyl-2-benzofurancarboxamide (4.11 g) in tetrahydrofuran (10 ml) dropwise at 0°C and the mixture was stirred for 3 hours under reflux. After cooling excess aluminum hydride was destroyed with diethyl ether saturated with water. Inorganic material was filtered off. Solvent was evaporated to leave the residue which was taken up in diethyl ether. The organic solution was washed with 1N aqueous sodium hydroxide, dried and evaporated to afford a residue which was dissolved in methanol (5 ml). To this solution was added 10% hydrochloric acid - methanol solution (5 ml). Methanol was evaporated to give a residue. Recrystallization from diethyl ether gave N-heptyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride (3.19 g).
NMR (CD_3OD, δ) : 0.91 (3H, t, J=7Hz), 1.30 (8H, br s), 1.62 (2H, m), 2.45 (3H, s), 3.00 (2H, t, J=7Hz), 4.47 (2H, s), 7.25-7.62 (7H, m)

Preparation 7

The following compounds were obtained according to a similar manner to that of Preparation 3.
(1) N-Benzyl-[5-chloro-3-(4-chlorophenyl)benzofuran-2-ylmethyl]amine
NMR ($CDCl_3$, δ) : 3.79 (2H, s), 3.95 (2H, s), 7.28-7.51 (12H, m)
(2) N-Benzyl-(3-phenylindol-2-ylmethyl)amine
NMR ($CDCl_3$, δ) : 3.78 (2H, s), 4.11 (2H, s), 7.08-7.45 (13H, m), 7.69 (1H, d, J=8Hz)
(3) N-Benzyl-[3-(4-chlorophenyl)-6-methylbenzofuran-2-ylmethyl]amine
NMR ($CDCl_3$, δ) : 2.50 (3H, s), 3.79 (2H, s), 3.98 (2H, s), 7.07-7.48 (12H, m)
(4) N-(2-Fluorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.85 (2H, s), 3.96 (2H, s), 6.95-7.36 (7H, m), 7.42 (4H, s)
(5) N-(3-Fluorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.76 (2H, s), 3.95 (2H, s), 6.88-7.37 (7H, m), 7.42 (4H, s)
(6) N-(4-Fluorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine
NMR ($CDCl_3$, δ) : 2.38 (3H, s), 4.02-4.11 (4H, m), 6.92 (2H, t, J=8Hz), 7.12 (1H, dd, J=2, 8Hz), 7.34-7.43

(8H, m)

(7) N-Cyclopropyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 0.37-0.42 (4H, m), 2.15 (1H, m), 2.43 (3H, s), 4.00 (2H, s), 7.12 (1H, dd, J=2, 8Hz), 7.32 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.46 (4H, s)

(8) N-Furfuryl-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.77 (2H, s), 3.95 (2H, s), 6.04 (1H, d, J=3Hz), 6.27 (1H, m), 7.13 (1H, dd, J=2, 8Hz), 7.33-7.42 (3H, m), 7.35 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)

(9) N-Furfuryl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.77 (2H, s), 3.95 (2H, s), 6.03 (1H, d, J=3Hz), 6.26 (1H, dd, J=2, 8Hz), 7.32-7.47 (7H, m)

(10) N-Furfuryl-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 2.43 (6H, s), 3.77 (2H, s), 3.98 (2H, s), 6.01 (1H, d, J=3Hz), 6.25 (1H, m), 7.11 (1H, dd, J=2, 8Hz), 7.29-7.40 (7H, m)

(11) N-Heptyl-[5-methyl-3-(4-propylphenyl)benzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.00 (3H, t, J=7Hz), 1.25 (8H, br s), 1.43 (2H, m), 1.72 (2H, tq, J=7, 7Hz), 2.42 (3H, s), 2.59 (2H, t, J=7Hz), 2.65 (2H, t, J=7Hz), 3.98 (2H, s), 7.09 (1H, dd, J=2, 8Hz), 7.30 (2H, d, J=8Hz), 7.38 (1H, d, J=2Hz), 7.38 (1H, d, J=8Hz), 7.41 (2H, d, J=8Hz)

(12) N-Heptyl-(6-phenylbenzofuran-2-ylmethyl)amine

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, br s), 1.48-1.60 (2H,m), 2.69 (2H, t, J=7Hz), 3.96 (2H, s), 6.59 (1H, s), 7.3-7.68 (8H, m)

(13) N-Heptyl-(7-phenylbenofuran-2-ylmethyl)amine

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (8H, br s), 1.49-1.60 (2H, m), 2.69 (2H, t, J=7Hz), 3.96 (2H, s), 6.63 (1H, s), 7.24-7.54 (6H, m), 7.84 (2H, dd, J=2, 8Hz)

(14) N-Heptyl-(3-phenylindol-2-ylmethyl)amine

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.27 (8H, br s), 1.48 (2H, br t, J=7Hz), 2.62 (2H, t, J=7Hz), 4.06 (2H, s), 7.06-7.48 (8H, m), 7.69 (1H, d, J=8Hz), 8.93 (1H, br s)

(15) N-Phenyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 4.45 (2H, s), 6.60 (2H, d, J=8Hz), 6.73 (1H, dd, J=8, 8Hz), 7.12-7.18 (3H, m), 7.32 (1H, d, J=2Hz), 7.37 (1H, d, J=8Hz), 7.43 (2H, d, J=8Hz), 7.47 (2H, d, J=8Hz)

Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 4.

(1) Ethyl [2-(4-bromobenzoyl)-4-methylphenoxy]acetate

NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 2.33 (3H, s), 4.17 (2H, q, J=7Hz), 4.49 (2H, s), 6.74 (1H, d, J=8Hz), 7.24 (2H, d, J=8Hz), 7.56 (2H, d, J=8Hz), 7.74 (2H, d, J=8Hz)

(2) Ethyl [2-(4-chlorobenzoyl)-4-chlorophenoxy]acetate

NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 4.19 (2H, q, J=7Hz), 4.52 (2H, s), 6.78 (1H, d, J=8Hz), 7.40-7.45 (4H, m), 7.81 (2H, d, J=8Hz)

(3) Ethyl [4-chloro-2-(4-methylbenzoyl)phenoxy]acetate

NMR ($CDCl_3$, δ) : 1.24 (3H, t, J=7Hz), 2.43 (3H, s), 4.19 (2H, q, J=7Hz), 4.55 (2H, s), 6.79 (1H, d, J=7Hz), 7.30-7.39 (4H, m), 7.78 (2H, d, J=7Hz)

(4) Ethyl [2-(4-chlorobenzoyl)-4,6-dimethylphenoxy]acetate

NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 2.30 (3H, s), 2.35 (3H, s), 4.16 (2H, q, J=7Hz), 4.38 (2H, s), 6.97 (1H, s), 7.18 (1H, s), 7.42 (2H, d, J=7Hz), 7.78 (2H, d, J=7Hz)

(5) Ethyl [2-(4-chlorobenzoyl)-4-ethylphenoxy]acetate

NMR ($CDCl_3$, δ) : 1.25 (6H, t, J=7Hz), 2.65 (2H, q, J=7Hz), 4.18 (2H, q, J=7Hz), 4.52 (2H, s), 6.78 (1H, d, J=7Hz), 7.25-7.30 (2H, m), 7.40 (2H, d, J=7Hz), 7.83 (2H, d, J=7Hz)

(6) Ethyl [2-(4-chlorobenzoyl)-5-methylphenoxy]acetate

NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=7Hz), 2.42 (3H, s), 4.19 (2H, q, J=7Hz), 4.52 (2H, s), 6.67 (1H, s), 6.93 (1H, d, J=8Hz), 7.35 (1H, d, J=8Hz), 7.40 (2H, d, J=7Hz), 7.82 (2H, d, J=7Hz)

(7) Ethyl [2-(4-chlorobenzoyl)-6-methylphenoxy]acetate

NMR ($CDCl_3$, δ) : 1.22 (3H, t, J=7Hz), 2.40 (3H, s), 4.28 (2H, q, J=7Hz), 4.40 (2H, s), 6.99-7.23 (2H, m), 7.34 - 7.43 (3H, m), 7.78 (2H, d, J=7Hz)

(8) Ethyl [2-(4-fluorobenzoyl)-4-methylphenoxy]acetate

MNR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 2.33 (3H, s), 4.16 (2H, q, J=7Hz), 4.51 (2H, s), 6.74 (1H, d, J=8Hz), 7.10 (2H, t, J=8Hz), 7.22 (1H, s), 7.23 (1H, d, J=8Hz), 7.90 (2H, dd, J=5, 8Hz)

(9) Ethyl (2-formyl-5-phenylphenoxy)acetate

NMR ($CDCl_3$, δ) : 1.32 (3H, t, J=7Hz), 4.30 (2H, q, J=7Hz), 4.83 (2H, s), 7.05 (1H, d, J=2Hz), 7.39-7.60 (6H, m), 7.95 (1H, d, J=8Hz), 10.59 (1H, s)
(10) Ethly (2-formyl-6-phenylphenoxy)acetate
NMR ($CDCl_3$, δ) : 1.20 (3H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 4.15 (2H, s), 7.31-7.60 (7H, m), 7.89 (1H, dd, J=2, 8Hz), 10.72 (1H, d, J=2Hz)

Preparation 9

The following compounds were obtained according to a similar manner to that of Preparation 5.
(1) 3-(4-Bromophenyl)-5-methyl-2-benzofurancarboxylic acid
NMR (DMSO-d_6, δ) : 2.39 (3H, s), 7.25 (1H, d, J=8Hz), 7.31 (1H, s), 7.55 (3H, d, J=8Hz), 7.64 (2H, d, J=8Hz)
(2) 3-(4-Chlorophenyl)-6-methyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 2.50 (3H, s), 7.10-7.17 (1H, m), 7.49 - 7.60 (6H, m)
(3) 5-Chloro-3-(4-chlorophenyl)-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 7.40-7.57 (7H, m)
(4) 5-Chloro-3-(4-methylphenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 2.20 (3H, s), 7.00-7.38 (7H, m)
(5) 5-Chloro-3-phenyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 7.35-7.53 (8H, m)
(6) 3-(4-Chlorophenyl)-5,7-dimethyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 2.38 (3H, s), 2.53 (3H, s), 7.14 (2H, d, J=7Hz), 7.45-7.57 (4H, m)
(7) 3-(4-Chlorophenyl)-5-ethyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 1.25 (3H, t, J=7Hz), 2.74 (2H, q, J=7Hz), 7.33-7.59 (7H, m)
(8) 3-(4-Chlorophenyl)-7-methyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 2.60 (3H, s), 7.20-7.58 (7H, m)
(9) 3-(4-Fluorophenyl)-5-methyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 2.10 (3H, s), 6.85-7.37 (7H, s)
(10) 6-Phenyl-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 7.31-7.83 (9H, m)
(11) 7-Phenyl-2-benzofurancarboxylic acid
NMR ($CDCl_3$-CD_3OD, δ) : 7.38-7.70 (7H, m), 7.89-7.93 (2H, m)

Preparation 10

The following compounds were obtained according to similar manners those of Preparations 1, 4 and 5.
(1) 3-(3,4-Dichlorophenyl)-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.28 (8H, br s), 1.58-1.70 (2H, m), 3.43 (2H, q, J=7Hz), 6.69 (1H, br t, J=7Hz), 7.30-7.38 (1H, m), 7.44-7.60 (5H, m), 7.75 (1H, s)
(2) 3-(3-Chlorophenyl)-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.57-1.65 (2H, m), 3.43 (2H, q, J=7Hz), 6.63 (1H, br t, J=7Hz), 7.28-7.66 (8H, m)
(3) 3-(2-Chlorophenyl)-N-heptyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.30 (8H, br s), 1.50-1.60 (2H, m), 2.52 (3H, s), 3.49 (2H, q, J=7Hz), 6.49 (1H, br s), 7.13-7.58 (7H, m)
(4) N-Heptyl-3-isopentyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 0.99 (6H, d, J=7Hz), 1.27-1.42 (8H, m), 1.53-1.72 (5H, m), 3.15 (2H, t, J=7Hz), 3.46 (2H, q, J=7Hz), 6.65 (1H, br t, J=7Hz), 7.23-7.47 (3H, m), 7.63 (1H, d, J=8Hz)

Preparation 11

The following compounds were obtained according to similar manners those of Preparations 4 and 5.
(1) 5-Isopropyl-3-phenyl-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 1.28 (6H, d, J=7Hz), 3.00 (1H, sep, J=7Hz), 7.38-7.62 (8H, m)
(2) 3,5-Diphenyl-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 7.30-7.79 (13H, m)
(3) 3-(2-Chlorophenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 7.30-7.70 (8H, m)

(4) 3-(4-Chlorophenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 7.25-7.70 (8H, m)
(5) 3-(2-Methylphenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 2.20 (3H, s), 7.27-7.68 (8H, m)
(6) 3-(3-Methylphenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 2.47 (3H, s), 7.28-7.67 (8H, m)
(7) 5-Methyl-3-(4-methylphenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.47 (3H, s), 7.28-7.37 (4H, m), 7.45-7.52 (3H, m)
(8) 3-(4-Methylphenyl)-2-benzofurancarboxylic acid
NMR (CD_3OD, δ) : 2.32 (3H, s), 7.17-7.52 (8H, m)
(9) 5-Methyl-3-phenyl-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 7.40-7.62 (8H, m)
(10) 5-Methyl-3-(4-propylphenyl)-2-benzofurancarboxylic acid
NMR ($CDCl_3$, δ) : 1.02 (3H, t, J=7Hz), 1.73 (2H, tq, J=7, 7Hz), 2.43 (3H, s), 2.68 (2H, t, J=7Hz), 7.30 (2H, d, J=8Hz), 7.32 (1H, dd, J=2, 8Hz), 7.40 (2H, d, J=1Hz), 7.51 (1H, d, J=8Hz), 7.51 (2H, d, J=8Hz)

Preparation 12

The following compounds were obtained according to a similar manner to that of Preparation 6.
(1) N-Benzyl-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]aminehydrochloride
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.77 (2H, s), 3.95 (2H, s), 7.13 (1H, dd, J=2, 8Hz), 7.22-7.41 (9H, m), 7.56 (2H, d, J=8Hz)
(2) N-Benzyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.43 (3H, s), 4.23 (2H, s), 4.45 (2H, s), 7.26-7.55 (12H, m)
(3) N-Benzyl-[3-(4-fluorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR ($CDCl_3$-CD_3OD, δ) : 2.46 (3H, s), 4.12 (2H, s), 4.32 (2H, s), 7.17-7.48 (12H, m)
(4) N-Benzyl-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.42 (6H, s), 4.22 (2H, s), 4.45 (2H, s), 7.23-7.51 (12H, m)
(5) N-Benzyl-[5-chloro-3-(4-methylphenyl)benzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.44 (3H, s), 4.24 (2H, s), 4.50 (2H, s), 7.35-7.65 (12H, m)
(6) N-(4-Methylbenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.37 (3H, s), 2.45 (3H, s), 4.20 (2H, s), 4.43 (2H, s), 7.19-7.30 (5H, m), 7.40-7.55 (6H, m)
(7) N-(2-Phenylethyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.43 (3H, s), 3.02 (2H, t, J=7Hz), 3.20 (2H, t, J=7Hz), 4.41 (2H, s), 7.16-7.56 (12H, m)
(8) N-(3,4-Dichlorobenzyl)-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 2.45 (3H, s), 4.15 (2H, s), 4.42 (2H, s), 7.24-7.60 (10H, m)
(9) N-Benzyl-(5-chloro-3-phenylbenzofuran-2-ylmethyl)amine hydrochloride
NMR (CD_3OD, δ) : 4.28 (2H, s), 4.50 (2H, s), 7.40-7.67 (13H, m)
(10) N-Cyclobutyl-(5-chloro-3-phenylbenzofuran-2-ylmethyl)amine hydrochloride
NMR (CD_3OD, δ) : 1.80-1.93 (2H, m), 2.06-2.21 (4H, m), 3.76 (1H, m), 4.38 (2H, S), 7.42-7.65 (8H, m)
(11) N-Cyclobutyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 1.77-1.94 (2H, m), 2.08-2.22 (4H, m), 2.43 (3H, s), 3.75 (1H, m), 4.34 (2H, s), 7.27 (1H, dd, J=2, 8Hz), 7.39 (1H, d, J=2Hz), 7.50 (1H, d, J=8Hz), 7.53-7.62 (4H, m)
(12) N-Cyclohexyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR (CD_3OD, δ) : 1.22-1.37 (6H, m), 1.80-1.87 (2H, m), 2.00-2.05 (2H, m), 2.43 (3H, s), 3.04 (1H, m), 4.47 (2H, s), 7.28 (1H, dd, J=2, 8Hz), 7.40 (1H, d, 3=2Hz), 7.50 (1H, d, J=8Hz), 7.54 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(13) N-Cyclopentyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]amine hydrochloride
NMR ($CDCl_3$, δ) : 1.43 (2H, m), 1.67-1.90 (6H, m), 2.39 (3H, s), 3.35 (1H, m), 4.23 (2H, t, J=5Hz), 7.16 (1H, dd, J=2, 8Hz), 7.26 (1H, d, J=2Hz), 7.42-7.57 (5H, m)
(14) N-Heptyl-(5-chloro-3-phenylbenzofuran-2-ylmethyl)amine
NMR (CD_3OD, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, br s), 1.62 (2H, m), 3.02 (2H, t, J=7Hz), 4.51 (2H, s), 7.42-7.66 (8H, m)

Preparation 13

To a mixture of 4-isopentylanisole (1.0 g) and tin(IV) chloride (1.3 ml) in methylene chloride (15 ml) was added 1,1-dichloromethyl ether (0.97 g) dropwise at 0°C and the mixture was stirred for 2 hours under reflux. After cooling the reaction mixture was poured into ice-cold water. The organic layer was washed with water and dried. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. Elution with chloroform gave 5-isopentyl-2-methoxybenzaldehyde (0.96 g).
NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.42-1.61 (3H, m), 2.58 (2H, t, J=7Hz), 3.91 (3H, s), 6.90 (1H, d, J=8Hz), 7.37 (1H, dd, J=2, 8Hz), 7.63 (1H, d, J=2Hz), 10.45 (1H, s)

Preparation 14

To a solution of 5-isopentyl-2-methoxybenzaldehyde (0.96 g) in methylene chloride (15 ml) was added boron tribromide (0.9 ml) dropwise at 0°C and the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured into water. The organic layer was washed with water and dried. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. Elution with chloroform gave 2-hydroxy-5-isopentylbenzaldehyde (0.72 g).
NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.43-1.67 (3H, m), 2.60 (2H, t, J=7Hz), 6.92 (1H, d, J=8Hz), 7.34-7.38 (2H, m), 9.88 (1H, s), 10.85 (1H, s)

Preparation 15

A mixture of 2-hydroxy-5-isopentylbenzaldehyde (0.72 g), diethyl bromomalonate (0.95 g) and potassium carbonate (1.1 g) in 2-butanone (10 ml) was stirred under reflux for 10 hours. After cooling potassium carbonate was filtered off, solvent was evaporated to give a residue which was taken up in diethyl ether and water. The organic layer was washed with water and dried. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with chloroform gave ethyl 5-isopentyl-2-benzofurancarboxylate (0.46 g).
NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.42 (3H, t, J=7Hz), 1.51-1.64 (3H, m), 2.71 (2H, t, J=7Hz), 4.44 (2H, q, J=7Hz), 7.27 (1H, dd, J=2, 8Hz), 7.46-7.51 (3H, m)

Preparation 16

A mixture of ethyl 5-isopentyl-2-benzofurancarboxylate (0.46 g) and 1N aqueous sodium hydroxide in methanol (5 ml) was stirred at 60°C for 1 hour. After cooling methanol was evaporated to leave a residue which was acidified with 1N hydrochloric acid and extracted with ethyl acetate, the extract was washed with water and dried. Evaporation of solvent gave 5-isopentyl-2-benzofurancarboxylic acid (0.36 g).
NMR (CD_3OD, δ) : 0.95 (6H, d, J=7Hz), 1.49-1.65 (3H, m), 2.70 (2H, t, J=7Hz), 7.19 (1H, dd, J=2, 8Hz), 7.25 (1H, s), 7.39-7.42 (2H, m), 7.54 (1H, s)

Preparation 17

To a stirred mixture of 5-methyl-3-(4-methylphenyl)-2-benzofurancarboxylic acid (456 mg) and N,N-dimethylformamide (1 drop) in methylene chloride (10 ml) was added oxalyl chloride (0.3 ml) at ambient temperature and the mixture was stirred at the same temperature for 2 hours. Oxalyl chloride was removed under reduced pressure to give 5-methyl-3-(4-methylphenyl)-2-benzofurancarbonyl chloride, which was dissolved in methylene chloride (10 ml). To this stirred solution was added triethylamine (0.5 ml) and then benzylamine (220 mg) dropwise at 0°C and the mixture was stirred at the same temperature for 15 minutes. The reaction mixture was washed with dilute hydrochloric acid and dilute aqueous sodium bicarbonate, and dried. Evaporation of solvent followed by recrystallization from n-hexane-ethyl acetate gave N-benzyl-5-methyl-3-(4-methylphenyl)-2-benzofurancarboxamide (0.55 g).
NMR ($CDCl_3$, δ) : 2.42 (6H, s), 4.60 (2H, d, J=5Hz), 6.80 (1H, br t, J=5Hz), 7.34-7.55 (12H, m)

Preparation 18

The following compounds were obtained according to a similar manner to that of Preparation 17.
(1) N-Benzyl-3-(4-bromophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.62 (2H, d, J=5Hz), 6.93 (1H, t, J=5Hz), 7.24-7.40 (8H, m), 7.54 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(2) N-Benzyl-5-chloro-3-(4-chlorophenyl)-2-benzofurancarboxamide

NMR ($CDCl_3$, δ) : 4.61 (2H, d, J=5Hz), 6.90 (1H, br t, J=5Hz), 7.45-7.61 (12H, m)
(3) N-Benzyl-3-(4-chlorophenyl)-6-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.50 (3H, s), 4.63 (2H, d, J=7Hz), 6.93 (1H, br t, J=7Hz), 7.12-7.50 (10H, m), 7.64 (2H, d, J=8Hz)
(4) N-Benzyl-3-(4-chlorophenyl)-7-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.66(2H, d, J=7Hz), 6.95 (1H, br t, J=7Hz), 7.21-7.39 (8H, m), 7.45 (2H, d, J=8Hz), 7.64 (2H, d, J=8Hz)
(5) N-Benzyl-5-chloro-3-(4-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.60 (2H, d, J=7Hz), 6.79 (1H, br t, J=7Hz), 7.28-7.58 (12H, m)
(6) N-Benzyl-3-(4-fluorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.61 (2H, d, J=5Hz), 6.90 (1H, br t, J=5Hz), 7.13-7.41 (10H, m), 7.65 (2H, dd, J=5, 8Hz)
(7) 5-Chloro-N-furfuryl-3-(4-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 4.61 (2H, d, J=7Hz), 6.26-6.29 (1H, m), 6.32-6.35 (1H, m), 6.82 (1H, br t, J=7Hz), 7.28-7.59 (8H, m)
(8) 3-(4-Chlorophenyl)-N-(3-fluorobenzyl)-5-methyl-2-benzofurancarboxamide
NMR($CDCl_3$, δ) : 2.44 (3H, s), 4.62 (2H, d, J=5Hz), 6.95-7.42 (8H, m), 7.45 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(9) 3-(4-chlorophenyl)-N-(4-methoxybenzyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 3.80 (3H, s), 4.55 (2H, d, J=7Hz), 6.83-6.90 (3H, m), 7.25-7.40 (4H, m), 7.45 (2H, d, J=7Hz), 7.61 (2H, d, J=7Hz)
(10) 3-(4-Chlorophenyl)-5-methyl-N-(4-methylbenzyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.38 (3H, s), 2.44 (3H, s), 4.58 (2H, d, J=5Hz), 6.88 (1H, br t, J=7Hz), 7.15-7.63 (11H, m)
(11) N-(4-Chlorobenzyl)-3-(4-chlorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.60 (2H, d, J=7Hz), 6.95 (1H, br t, J=7Hz), 7.30-7.65 (11H, m)
(12) 3-(4-chlorophenyl)-N-[2-(1-cyclohexenyl)ethyl]-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.59 (6H, s), 1.95 (2H, br s), 2.22 (2H, t, J=7Hz), 2.45 (3H, s), 3.49 (2H, q, J=7 Hz), 5.50 (1H, s), 6.59 (1H, t, J=7Hz), 7.28-7.60 (7H, m)
(13) 3-(4-chlorophenyl)-N-(4-fluorobenzyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.58 (2H, d, J=5Hz), 6.93 (1H, t, J=5Hz), 7.03 (2H, t, J=8Hz), 7.29-7.42 (5H, m), 7.45 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(14) 3-(4-chlorophenyl)-N-(3-furylmethyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 4.47 (2H, d, J=5Hz), 6.43 (1H, s), 6.79 (1H, br t, J=5Hz), 7.28-7.48 (7H, m), 7.61 (2H, d, J=8Hz)
(15) 3-(4-Chlorophenyl)-5-methyl-N-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 7.14 (1H, dd, J=8, 8Hz), 7.32-7.66 (11H, m), 8.37 (1H, s)
(16) 3-(4-Chlorophenyl)-5-methyl-N-(2-phenylethyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 2.92 (2H, t, J=7Hz), 3.68 (2H, dt, J=7, 5Hz), 6.67 (1H, t, J=5Hz), 7.20-7.41 (8H, m), 7.43 (2H, d, J=8Hz), 7.57 (2H, d, J=8Hz)
(17) 3-(4-Chlorophenyl)-5-methyl-N-(3-phenylpropyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.95 (2H, q, J=7Hz), 2.43 (3H, s), 2.70 (2H, t, J=7Hz), 3.48 (2H, q, J=7Hz), 6.63 (1H, br t, J=7Hz), 7.21-7.62 (12H, m)
(18) 3-(4-Chlorophenyl)-5-methyl-N-(4-pyridylmethyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.48 (3H, s), 4.66 (2H, d, J=7Hz), 7.10 (1H, t, J=7Hz), 7.28-7.63 (9H, m), 8.58 (2H, d, J=7Hz)
(19) 3-(4-Chlorophenyl)-5-methyl-N-(2-thienylmethyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.80 (2H, d, J=7Hz), 6.88-7.05 (3H, m), 7.24-7.42 (3H, m), 7.47 (2H, d, J=7Hz), 7.60 (2H, d, J=7Hz)
(20) 3-(4-Chlorophenyl)-N-(3,4-dichlorobenzyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.55 (2H, d, J=5Hz), 7.00 (1H, t, J=5Hz), 7.19 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.35-7.44 (4H, m), 7.47 (2H, d, J=8Hz), 7.61 (2H, d, J=8Hz)
(21) 3-(4-Chlorophenyl)-5-methyl-N-(2-pyridylmethyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 4.73 (2H, d, J=5Hz), 7.20-7.72 (10H, m), 7.80 (1H, t, J=5Hz), 8.56 (1H, d, J=5Hz)
(22) 3-(4-chlorophenyl)-5-methyl-N-(3-pyridylmethyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.48 (3H, s), 4.65 (2H, d, J=7Hz), 7.02 (1H, br t, J=7Hz), 7.28-7.75 (9H, m), 8.52-8.65 (2H, m)
(23) N-Benzyl-5-chloro-3-phenyl-2-benzofurancarboxamide

NMR ($CDCl_3$, δ) : 4.62 (2H, d, J=7Hz), 6.82 (1H, br t, J=7Hz), 7.33-7.65 (13H, m)
(24) 5-Chloro-N-cyclobutyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.68-2.04 (4H, m), 2.32-2.46 (2H, m), 4.55 (1H, m), 7.37-7.62 (8H, m)
(25) 3-(4-Chlorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 5.72 (1H, br s), 6.45 (1H, br s), 7.27-7.47 (3H, m), 7.48 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)
(26) 3-(4-Chlorophenyl)-N-cyclobutyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.67-1.84 (2H, m), 1.90-2.10 (2H, m), 2.33-2.48 (2H, m), 2.42 (3H, s), 4.53 (1H, m), 6.75 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.44 (2H, d, J=9Hz), 7.59 (2H, d, J=9Hz)
(27) 3-(4-Chlorophenyl)-N-cyclopropyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.60-0.68 (2H, m), 0.82-0.92 (2H, m), 2.43 (3H, s), 2.86 (1H, m), 6.73 (1H, d, J=3Hz), 7.28-7.42 (3H, m), 7.46 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(28) 3-(4-Chlorophenyl)-N-cyclohexyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.16-1.50 (6H, m), 1.62-1.80 (2H, m), 1.97-2.03 (2H, m), 2.43 (3H, s), 3.93 (1H, m), 6.50 (1H, d, J=8Hz), 7.24-7.41 (3H, m), 7.44 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)
(29) 3-(4-Chlorophenyl)-N-cyclopentyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.46-1.77 (6H, m), 1.98-2.14 (2H, m), 2.43 (3H, s), 4.35 (1H, m), 6.54 (1H, d, J=7Hz), 7.27 (1H, dd, J=2, 8Hz), 7.33 (1H, d, J=2Hz), 7.42 (1H, d, J=8Hz), 7.45 (2H, d, J=8Hz), 7.61 (2H, d, J=8Hz)
(30) 3-(4-Chlorophenyl)-N-cyclohexylmethyl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.85-1.05 (2H, m), 1.10-1.28 (3H, m), 1.65-1.80 (6H, m), 2.48 (3H, s), 3.28 (2H, t, J=7Hz), 6.69 (1H, br t, J=7Hz), 7.30-7.50 (5H, m), 7.60 (2H, d, J=7Hz)
(31) 5-Chloro-N-cyclopentyl-3-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 1.38-1.52 (2H, m), 1.58-1.70 (4H, m), 1.94-2.09 (2H, m), 4.37 (1H, sext, J=7Hz), 6.49 (1H, br d, J=7Hz), 7.38-7.62 (8H, m)
(32) 3-(4-Chlorophenyl)-5-methyl-N-propyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.98 (3H, t, J=7Hz), 1.62 (2H, sext, J=7Hz), 2.43 (3H, s), 3.39 (2H, q, J=7Hz), 6.67 (1H, br t, J=7Hz), 7.27-7.40 (3H, m), 7.47 (2H, d, J=7Hz), 7.60 (2H, d, J=7Hz)
(33) 3-(4-Chlorophenyl)-5-ethyl-N-heptyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (11H, br s), 1.55-1.65 (2H, m), 2.74 (2H, q, J=7Hz), 3.42 (2H, q, J=7Hz), 6.62 (1H, br t, J=7Hz), 7.28-7.63 (7H, m)
(34) N-(2-Fluorobenzyl)-3-(4-chlorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.67 (2H, d, J=5Hz), 6.93 (1H, t, J=5Hz), 7.12 (2H, t, J=8Hz), 7.24-7.40 (5H, m), 7.46 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)
(35) N-Furfuryl-3-(4-bromophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.61 (2H, d, J=5Hz), 6.28-6.35 (2H, m), 6.92 (1H, t, J=5Hz), 7.29-7.43 (4H, m), 7.53 (2H, d, J=8Hz), 7.62 (2H, d, J=8Hz)
(36) 3-(4-Fluorophenyl)-N-furfuryl-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.42 (3H, s), 4.60 (2H, d, J=7Hz), 6.28-6.36 (2H, m), 6.91 (1H, br t, J=7Hz), 7.12-7.42 (6H, m), 7.58-7.69 (2H, m)
(37) N-Furfuryl-3-(4-chlorophenyl)-5-methyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.62 (2H, d, J=6Hz), 6.32 (2H, m), 6.92 (1H, t, J=6Hz), 7.28-7.43 (4H, m), 7.45 (2H, d, J=8Hz), 7.60 (2H, d, J=8Hz)
(38) N-Furfuryl-5-methyl-3-(4-methylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 2.42 (6H, s), 4.59 (2H, d, J=5Hz), 6.27 (1H, d, J=3Hz), 6.33 (1H, m), 6.83 (1H, t, J=5Hz), 7.23-7.43 (6H, m), 7.52 (2H, d, J=8Hz)
(39) N-Heptyl-6-phenylbenzofuran-2-carboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, br s), 1.60-1.75 (2H, m), 3.50 (2H, q, J=7Hz), 6.65 (1H, br t, J=7Hz), 7.33-7.77 (9H, m)
(40) N-Heptyl-7-phenyl-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.28-1.42 (8H, m), 1.55-1.67 (2H, m), 3.47 (2H, q, J=7Hz), 6.55 (1H, br t, J=7Hz), 7.35-7.83 (9H, m)
(41) N-Heptyl-3-phenylindole-2-carboxamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.06-1.37 (10H, m), 3.29 (2H, q, J=7Hz), 5.94 (1H, t, J=7Hz), 7.12 (1H, t, J=8Hz), 7.33 (1H, t, J=8Hz), 7.43-7.55 (7H, m), 9.45 (1H, s)
(42) 5-Methyl-N-heptyl-3-(4-propylphenyl)-2-benzofurancarboxamide
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.00 (3H, t, J=7Hz), 1.29 (8H, br s), 1.54 (2H, m), 1.72 (2H, tq, J=7, 7Hz), 2.42 (3H, s), 2.64 (2H, t, J=7Hz), 3.38 (2H, dt, J=7, 5Hz), 6.46 (1H, t, J=5Hz), 7.24 (1H, dd,

J = 2, 8Hz), 7.31 (2H, d, J = 8Hz), 7.35 (1H, d, J = 2Hz), 7.42 (1H, d, J = 8Hz), 7.54 (2H, d, J = 8Hz)

Preparation 19

To a stirred solution of 3-phenylindole-2-carboxylic acid (0.5 g) and benzylamine (0.23 g) in methylene chloride (10 ml) was added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.45 g) in some portions at 0°C and the mixture was stirred at abient temperature for 2 hours. The reaction mixture was washed with 3% aqueous hydrochloric acid (10 ml) and 3% aqueous sodium bicarbonate (10 ml), and dried. Evaporation of solvent gave a residue which was recrystallized from n-hexane-ethyl acetate to provide N-benzyl-3-phenylindole-2-carboxamide (0.52 g).
NMR ($CDCl_3$, δ) : 4.51 (2H, d, J = 5.5Hz), 6.30 (1H, t, J = 5.5Hz), 7.10-7.48 (14H m)

Example 1

To a stirred solution of N-heptyl-(3-phenyl-2-benzo[b]thiophen-2-ylmethyl)amine (2.60 g) in chloroform (30 ml) was added 2,4-difluorophenyl isocyanate (1.25 g) dropwise at 0°C and the mixture was stirred at ambient temperature for 1 hour. The solvent was evaporated to leave the residue which was chromatographed on silica gel. Elution with chloroform gave N-(2,4-difluorophenyl)-N'-heptyl-N'-(3-phenylbenzo[b]-thiophen-2-ylmethyl)urea (4.10 g) as an oil.
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J = 7Hz), 1.22 (8H, m), 1.48 (2H, m), 3.20 (2H, t, J = 7Hz), 4.79 (2H, s), 6.40 (1H, d, J = 3Hz), 6.74-6.88 (2H, m), 7.31-7.53 (8H, m), 7.83 (1H, m), 8.05 (1H, m)

Example 2

To a stirred suspension of lithium aluminum hydride (0.27 g) and aluminum chloride (0.32 g) in tetrahydrofuran (20 ml) was added a solution of N-heptyl-3-phenyl-2-benzofurancarboxamide (1.98 g) in tetrahydrofuran (10 ml) dropwise at 0°C and the mixture was refluxed for 3 hours. After cooling excess aluminum hydride was destroyed with diethyl ether saturated with water and filtered off. The organic solution was condensed to afford the residue which was taken up in diethyl ether and 1N aqueous sodium hydroxide. The organic solution was dried and evaporated to give N-heptyl-(3-phenylbenzofuran-2-yl-methyl)amine (1.89 g).

To a solution of N-heptyl-(3-phenylbenzofuran-2-ylmethyl)amine (1.89 g) in chloroform (30 ml) was added 2,4-difluorophenyl isocyanate (0.92 g) dropwise at 0°C and the mixture was stirred at ambient temperature for 1 hour. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with chloroform provided N-(2,4-difluorophenyl)-N'-heptyl-N'-(3-phenylbenzofuran-2-ylmethyl)urea (2.4 g).
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J = 7Hz), 1.15 (8H, m), 1.43 (2H, m), 3.22 (2H, t, J = 7Hz), 4.77 (2H, s), 6.80-6.89 (2H, m), 6.98 (1H, d, J = 3Hz), 7.23-7.60 (9H, m), 7.99 (1H, m)

Example 3

The following compounds were obtained according to a similar manner to that of Example 2.

(1) N-Benzyl-N-[3-(4-chlorophenyl)-7-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 164-165.5°C
NMR ($CDCl_3$, δ) : 2.58 (3H, s), 4.42 (2H, s), 4.70 (2H, s), 6.48 (1H, br s), 6.75 (2H, t, J = 7Hz), 6.99-7.04 (2H, m), 7.19-7.27 (6H. m), 7.37 (2H, d, J = 8Hz), 7.48 (2H, d, J = 8Hz)

(2) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3-furylmethyl)-N'-(2,4,6-trifluorophenyl)urea
mp : 173-175°C
NMR ($CDCl_3$, δ) : 2.46 (3H, s), 4.27 (2H, s), 4.69 (2H, s), 6.25 (1H, s), 6.59 (1H, s), 6.74 (2H, t, J = 8Hz), 6.99 (1H, s), 7.18-7.52 (8H, m)

(3) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-pyridylmethyl)-N'-(2,4,6-trifluorophenyl)-urea
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.43 (2H, s), 4.65 (2H, s), 6.78 (2H, t, J = 8Hz), 6.94 (1H, br s), 7.20-7.35 (6H, m), 7.49 (3H, t, J = 8Hz), 8.40-8.60 (2H, m)

(4) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-[2-(1-cyclohexenyl)ethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 169.5-170.5°C
NMR ($CDCl_3$, δ) : 1.50 (4H, br s), 1.75 (2H, br s), 1.90 (2H, br s), 2.08 (2H, t, J = 7Hz), 2.45 (3H, s), 3.29

(2H, t, J=7Hz), 4.75 (2H, s), 5.30 (1H, s), 6.45 (1H, br s), 6.72 (2H, t, J=7Hz), 7.28-7.51 (7H, m)

(5) N-[5-Chloro-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N-furfuryl-N'-(2,4,6-trifluorophenyl)urea

mp : 151-152.5 °C

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.43 (2H, s), 4.80 (2H, s), 5.85 (1H, d, J=2Hz), 6.20-6.24 (1H, m), 6.62 (1H, s), 6.72 (2H, t, J=8Hz), 7.28-7.46 (7H, m), 7.51 (1H, d, J=2Hz)

(6) N-[3-(4-Fluorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-furfuryl-N'-(2,4,6-trifluorophenyl)urea

mp : 158.5-161 °C

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.42 (2H, s), 4.78 (2H, s), 5.90 (1H, d, J=3Hz), 6.23 (1H, dd, J=3, 1Hz), 6.72 (1H, s), 6.73 (2H, d, J=7Hz), 7.16-7.50 (8H, m)

(7) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3-phenylpropyl)-N'-(2,4,6-trifluorophenyl)-urea

mp : 84-86 °C

NMR ($CDCl_3$, δ) : 1.79 (2H, qui, J=7Hz), 2.47 (3H, s), 2.50 (2H, t, J=7Hz), 3.30 (2H, t, J=7Hz), 4.73 (2H, s), 6.39 (1H, br s), 6.73 (2H, t, J=7Hz), 6.99-7.06 (2H, m), 7.15-7.50 (10H, m)

(8) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(2-thienylmethyl)-N'-(2,4,6-trifluorophenyl)-urea

mp : 179-181 °C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.60 (2H, s), 4.70 (2H, s), 6.60-6.63 (2H, m), 6.74 (2H, t, J=7Hz), 7.18-7.51 (8H, m)

(9) N-Heptyl-N-(3-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.17 (8H, s), 1.43 (2H, m), 3.23 (2H, t, J=7Hz), 4.77 (2H, s), 6.45 (1H, s), 6.72 (2H, t, J=8Hz), 7.28-7.62 (9H, m)

(10) N-Heptyl-N-(5-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.28-1.35 (8H, m), 1.67 (2H, m), 3.44 (2H, t, J=7Hz), 4.69 (2H, s), 6.32 (1H, s), 6.73 (2H, t, J=8Hz), 7.32-7.75 (9H, m)

(11) N-(Benzofuran-2-ylmethyl)-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.30 (8H, br s), 1.58-1.70 (2H, m) 3.44 (2H, t, J=7Hz), 4.68 (2H, s), 6.34 (1H, s), 6.71 (2H, t, J=7Hz), 7.20-7.34 (3H, m), 7.45-7.58 (2H, m)

MASS (m/z) : 419 (M+)

(12) N-Cycloheptyl-N-(3-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 1.39-1.50 (10H, m), 1.67-1.78 (2H, m), 4.10 (1H, br s), 4.75 (2H, s), 6.72 (2H, t, J=7Hz), 6.90 (1H, s), 7.29-7.63 (9H, m)

(13) N-[3-(3,4-Dichlorophenyl)benzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.19 (8H, br s), 1.45-1.54 (2H, m), 3.28 (2H, t, J=7Hz), 4.78 (2H, s), 6.33 (1H, s), 6.74 (2H, t, J=7Hz), 7.30-7.42 (3H, m), 7.52-7.63 (4H, m)

(14) N-[3-(3-Chlorophenyl)benzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.18 (8H, br s), 1.40-1.53 (2H, m), 3.27 (2H, t, J=7Hz), 4.30 (2H, s), 6.39 (1H, s), 6.75 (2H, t, J=7Hz), 7.30-7.60 (8H, m)

(15) N-Heptyl-N-(5-isopropyl-3-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.14 (8H, br s), 1.28 (6H, d, J=7Hz), 1.39-1.50 (2H, m), 3.01 (1H, sep, J=7Hz), 3.22 (2H, t, J=7Hz), 4.75 (2H, s), 6.49 (1H, br s), 6.68-6.80 (2H, m), 7.23-7.53 (8H, m)

(16) N-[3-(2-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.16 (8H, br s), 1.32-1.48 (2H, m), 2.40 (3H, s), 3.22 (2H, t, J=7Hz), 4.62 (2H, ABq, J=15, 14Hz), 6.47 (1H, s), 6.75 (2H, t, J=7Hz), 7.11-7.20 (2H, m), 7.39-7.60 (5H, m)

(17) N-Heptyl-N-(5-methyl-3-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.10 (8H, br s), 1.38-1.50 (2H, m), 2.45 (3H, s), 3.24 (2H, t, J=7Hz), 4.74 (2H, s), 6.48 (1H, s), 6.72 (2H, t, J=7Hz), 7.16-7.53 (8H, m)

(18) N-(3,5-Diphenylbenzofuran-2-ylmethyl)-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.18 (8H, br s), 1.36-1.53 (2H, m), 3.26 (2H, t, J=7Hz), 4.83 (2H, s), 6.44 (1H, s), 6.75 (2H, t, J=7Hz), 7.40-7.78 (13H, m)

(19) N-[3-(2-Chlorophenyl)benzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.17 (8H, s), 1.38-1.47 (2H, m), 3.22 (2H, t, J=7Hz), 4.64 (2H, ABq, J=15Hz), 6.44 (1H, s), 6.73 (2H, t, J=7Hz), 7.28-7.40 (6H, m), 7.52-7.60 (2H, m)

(20) N-[3-(4-Chlorophenyl)benzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.15 (8H, br s), 1.40-1.50 (2H, m), 3.24 (2H, t, J=7Hz), 4.79 (2H, s), 6.37 (1H, s), 6.70 (2H, t, J=7Hz), 7.28-7.58 (8H, m)

(21) N-Heptyl-N-[3-(2-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.18 (8H, br s), 1.35-1.48 (2H, m), 2.20 (3H, s), 3.11-3.30 (2H, m), 4.59 (2H, ABq, J=15Hz), 6.48 (1H, s), 6.75 (2H, t, J=7Hz), 7.20-7.58 (8H, m)

(22) N-Heptyl-N-[3-(3-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.18 (8H, br s), 1.48-1.50 (2H, m), 2.45 (3H, s), 3.28 (2H, t, J=7Hz), 4.79 (2H, s), 6.45 (1H, s), 6.73 (2H, t, J=7Hz), 7.20-7.62 (8H, m)

(23) N-Heptyl-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.14 (8H, br s), 1.41 (2H, m), 2.42 (6H, s), 3.24 (2H, t, J=7Hz), 4.73 (2H, s), 6.50 (1H, s), 6.71 (2H, t, J=8Hz), 7.15 (1H, dd, J=2, 8Hz), 7.28-7.42 (6H, m)

(24) N-Heptyl-N-[3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.13 (8H, br s), 1.42 (2H, m), 2.43 (3H, s), 3.24 (2H, t, J=7Hz), 4.77 (2H, s), 6.47 (1H, br s), 6.72 (2H, t, J=8Hz), 7.23-7.60 (8H, m)

(25) N-Heptyl-N-(3-isopentylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 0.98 (6H, d, J=7Hz), 1.23-1.32 (8H, m), 1.50-1.70 (5H, m), 2.72 (2H, t, J=7Hz), 3.38 (2H, t, J=7Hz), 4.65 (2H, s), 6.72 (2H, t, J=8Hz), 7.21-7.56 (4H, m)

(26) N-Heptyl-N-(5-isopentylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 0.94 (6H, d, J=7Hz), 1.24-1.34 (8H, m), 1.47-1.67 (5H, m), 2.70 (2H, t, J=7Hz), 3.42 (2H, t, J=7Hz), 4.63 (2H, s), 6.37 (1H, s), 6.72 (2H, t, J=8Hz), 7.11 (1H, dd, J=2, 8Hz), 7.33-7.38 (3H, m)

(27) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-methoxybenzyl)-N'-(2,4,6-trifluorophenyl)urea

mp : 149.5-153.5 °C

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 3.79 (3H, s), 4.39 (2H, s), 4.67 (2H, s), 6.61-6.93 (6H, m), 7.18-7.50 (8H, m)

(28) N-(4-Chlorobenzyl)-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)-urea

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 4.48 (2H, s), 4.63 (2H, s), 6.76 (3H, t, J=7Hz), 6.99 (2H, d, J=7Hz), 7.15-7.25 (3H, m), 7.33-7.50 (6H, m)

(29) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(2-pyridylmethyl)-N'-(2,4,6-trifluorophenyl)-urea

mp : 143-144 °C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.50 (2H, s), 4.89 (2H, s), 6.74 (2H, t, J=8Hz), 7.12-7.47 (10H, m), 8.51 (1H, d, J=4Hz)

(30) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3-pyridyl)-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.43 (2H, s), 4.62 (2H, s), 6.70-6.83 (3H, m), 7.12-7.56 (9H, m), 8.24 (1H, s), 8.49 (1H, d, J=7Hz)

(31) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

mp : 234 °C

NMR ($CDCl_3$, δ) : 4.64 (2H, d, J=5Hz), 6.72 (2H, t, J=8Hz), 7.27-7.47 (7H, m)

(32) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cycloheptyl-N'-(2,4,6-trifluorophenyl)urea

mp : 54-58 °C

NMR ($CDCl_3$, δ) : 1.30 (10H, br s), 1.66-1.79 (2H, m), 2.47 (3H, s), 4.03-4.12 (1H, m), 4.70 (2H, s), 6.86 (1H, s), 6.72 (2H, t, J=7Hz), 7.17-7.56 (7H, m)

(33) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclohexylmethyl-N'-(2,4,6-trifluorophenyl)-urea

NMR ($CDCl_3$, δ) : 0.78-0.90 (3H, m), 1.03-1.13 (4H, m), 1.44-1.67 (4H, m), 2.45 (3H, s), 3.09 (2H, d, J=7Hz), 4.74 (2H, s), 6.40 (1H, br s), 6.70 (2H, t, J=7Hz), 7.13-7.51 (7H, m)

(34) N-(5-Chloro-3-phenylbenzofuran-2-ylmethyl)-N-cyclopentyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 1.40 (6H, br s), 1.75-1.85 (2H, m), 4.38-4.54 (1H, m), 4.78 (2H, s), 6.59 (1H, s), 6.72 (2H, t, J=7Hz), 7.29-7.58 (8H, m)

(35) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-pentyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.80 (3H, t, J=7Hz), 1.17 (4H, br s), 1.48-1.51 (2H, m), 2.47 (3H, s), 3.22 (2H, t, J=7Hz), 4.73 (2H, s), 6.40 (1H, s), 6.72 (2H, t, J=7Hz), 7.16-7.52 (7H, m)

(36) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-nonyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.16 (12H, br s), 1.40-1.50 (2H, m), 2.44 (3H, s), 3.25 (2H, t, J=7Hz), 4.77 (2H, s), 6.39 (1H, s), 6.72 (2H, t, J=7Hz), 7.18-7.52 (7H, m)

(37) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-propyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.82 (3H, t, J=7Hz), 1.40-1.59 (2H, m), 2.44 (3H, s), 3.23 (2H, t, J=7Hz), 4.74 (2H, s), 6.39 (1H, s), 6.72 (2H, t, J=7Hz), 7.15-7.52 (7H, m)

(38) N-[3-(4-Chlorophenyl)-5,7-dimethylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.18 (8H, br s), 1.40-1.50 (2H, m), 2.41 (3H, s), 2.54 (3H, s), 3.25 (2H, t, J=7Hz), 4.77 (2H, s), 6.31 (1H, s), 6.72 (2H, t, J=7Hz), 7.01 (1H, s), 7.15 (1H, s), 7.46 (4H, dd, J=7, 5Hz)
(39) N-[3-(4-Chlorophenyl)-5-ethylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.18 (11H, br s), 1.39-1.50 (2H, m), 2.66 (2H, q, J=7Hz), 3.24 (2H, t, J=7Hz), 4.75 (2H, s), 6.40 (1H, s), 6.73 (2H, t, J=7Hz), 7.20-7.33 (2H, m), 7.42-7.52 (5H, m)
(40) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(4-nitrophenyl)urea
mp : 141-142°C
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.20 (8H, s), 1.49 (2H, t, J=7Hz), 2.43 (3H, s), 3.28 (2H, t, J=7Hz), 4.72 (2H, s), 6.99 (1H, s), 7.19 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.41 (2H, d, J=9Hz), 7.41 (1H, d, J=8Hz), 7.45 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 8.16 (2H, d, J=9Hz)
(41) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,6-diisopropylphenyl)urea
mp : 172-173°C
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.17 (20H, br s), 1.48 (2H, t, J=7Hz), 2.43 (3H, s), 3.08 (2H, m), 3.32 (2H, t, J=7Hz), 4.77 (2H, s), 6.04 (1H, s), 7.17-7.45 (10H, m)

Example 4

To a stirred solution of 2,4,6-trifluoroaniline (335 mg) in ethyl acetate (10 ml) was added trichloromethyl chloroformate (258 mg) dropwise at ambient temperature and the mixture was stirred under reflux for 3 hours. To this mixture was added a solution of N-heptyl-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-amine (817 mg), prepared by treating the corresponding hydrochloride with 1N aqueous sodium hydroxide, in ethyl acetate (2 ml) dropwise at 0° and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was washed with 1N aqueous sodium hydroxide, 1N hydrochloric acid and saturated aqueous sodium bicarbonate, and dried. Evaporation of solvent gave a residue which was purified by column chromatography on silica gel. Elution with ethyl acetate-hexane (1:10) gave N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trifluorophenyl)urea (724 mg).
NMR ($CDCl_3$, δ) : 7.52-7.15 (7H, m), 6.74 (2H, t, J=7Hz), 6.40 (1H, s), 4.77 (2H, s), 3.25 (2H, t, J=7Hz), 2.46 (3H, s), 1.52-1.38 (2H, m), 1.18 (8H, br s), 0.85 (3H, t, J=7Hz)

Example 5

The following compounds were obtained according to a similar manner to that of Example 1.
(1) N-Benzyl-N-[5-chloro-3-(4-chlorophenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 166-167°C
NMR ($CDCl_3$, δ) : 4.46 (2H, s), 4.72 (2H, s), 6.38 (1H, br s), 6.72 (2H, t, J=8Hz), 7.00-7.04 (2H, m), 7.23-7.48 (10H, m)
(2) N-Benzyl-N-(3-phenylindol-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea
mp : 173-174.5°C
NMR ($CDCl_3$, δ) : 4.43 (2H, s), 4.75 (2H, s), 5.75 (1H, s), 6.72 (2H, t, J=8Hz), 7.02-7.43 (13H, m) 7.62 (1H, d, J=8Hz), 9.22 (1H, s)
(3) N-Benzyl-N-[3-(4-chlorophenyl)-6-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 179.5-181°C
NMR ($CDCl_3$, δ) : 2.53 (3H, s), 4.44 (2H, s), 4.69 (2H, s), 6.63 (1H, br s), 6.75 (2H, t, J=8Hz), 6.99-7.03 (2H, m), 7.11-7.48 (10H, m)
(4) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-furfuryl-N'-(2,4,6-triflurophenyl)urea
mp : 146-146.5°C
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.43 (2H, s), 4.77 (2H, s), 5.92 (1H, d, J=3Hz), 6.72 (1H, br s), 6.72 (2H, t, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.30 (2H, s), 7.42 (1H, d, J=8Hz), 7.42 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz)
(5) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(2-fluorobenzyl)-N'-(2,4,6-triflurophenyl)urea
mp : 157-158°C
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.57 (2H, s), 4.73 (2H, s), 6.58 (1H, s), 6.73 (2H, t, J=8Hz), 7.00 (2H, q, J=8Hz), 7.12-7.27 (4H, m), 7.34 (2H, d, J=8Hz), 7.41 (1H, d, J=8Hz), 7.43 (2H, d, J=8Hz)
(6) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3-fluorobenzyl)-N'-(2,4,6-triflurophenyl)urea
mp : 162-163°C
NMR ($CDCl_3$, δ) : 2.45 (3H, s), 4.42 (2H, s), 4.65 (2H, s), 6.69-6.78 (5H, m), 6.92 (1H, dt, J=2, 8Hz), 7.13-

7.35 (6H, m), 7.45 (2H, t, J=8Hz)

(7) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-fluorobenzyl)-N'-(2,4,6-trifluorophenyl)urea
mp : 171-172°C
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.35 (2H, s), 4.61 (2H, s), 6.71 (1H, s), 6.73 (2H, t, J=8Hz), 6.89-6.92 (4H, m), 7.18-7.50 (7H, m)

(8) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-phenyl-N'-(2,4,6-trifluorophenyl)urea
mp : 180-182.5°C
NMR ($CDCl_3$, δ) : 2.41 (3H, s), 5.12 (2H, s), 5.56 (1H, s), 6.71 (2H, t, J=8Hz), 7.02 (2H, d, J=8Hz), 7.11-7.43 (10H, m)

(9) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclopropyl-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.80-0.82 (4H, m), 2.42 (3H, s), 2.58 (1H, m), 4.82 (2H, s), 6.62 (1H, s), 6.72 (2H, t, J=8Hz), 7.13 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=2Hz), 7.40 (1H, d, J=8Hz), 7.47 (4H, s)

(10) N-Furfury-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 154-155°C
NMR ($CDCl_3$, δ) : 2.43 (6H, s), 4.42 (2H, s), 4.75 (2H, s), 5.83 (1H, d, J=3Hz), 6.21 (1H, m), 6.71 (2H, t, J=8Hz), 7.16 (1H, dd, J=2, 8Hz), 7.28-7.42 (7H, m)

(11) N-Heptyl-N-(7-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.29 (8H, br s), 1.61-1.76 (2H, m), 3.45 (2H, t, J=7Hz) 4.71 (2H, s), 6.00 (1H, s), 6.70 (2H, t, J=7Hz), 6.70 (1H, s), 7.29-7.56 (6H, m) 7.81 (2H, dd, J=2, 8Hz)

(12) N-Heptyl-N-(3-phenylindol-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea
mp : 122-123.5°C
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.13-1.23 (8H, m), 1.42 (2H, br t, J=7Hz), 3.08 (2H, t, J=7Hz) 4.69 (2H, s), 5.72 (1H, s), 6.77 (2H, t, J=8Hz) 7.12 (1H, td, J=2, 8Hz), 7.33-7.49 (6H, m) 7.63 (1H, d, J=8Hz), 9.34 (1H, s)

(13) N-Heptyl-N-(6-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.25 (8H, br s), 1.60-1.75 (2H, m), 3.45 (2H, t, J=7Hz), 4.70 (2H, s), 6.34 (1H, s), 6.72 (1H, s), 6.75 (2H, t, J=8Hz), 7.33-7.70 (8H, m)

(14) N-Heptyl-N-[5-methyl-3-(4-propylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 0.98 (3H, t, J=7Hz), 1.13 (8H, br s), 1.42 (2H, m), 1.70 (2H, tq, J=7, 7Hz), 2.43 (3H, s), 2.65 (2H, t, J=7Hz), 3.23 (2H, t, J=7Hz), 4.75 (2H, s), 6.47 (1H, s), 6.72 (2H, t, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.32 (2H, d, J=8Hz), 7.37-7.42 (4H, m)

(15) N-[3-(4-Bromophenyl)-5-methylbenzofuran-2-ylmethyl]-N-furfuryl-N'-(2,4,6-trifluorophenyl)urea
mp : 144°C
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 4.43 (2H, s), 4.77 (2H, s), 5.92 (1H, d, J=4Hz), 6.23 (1H, m), 6.72 (1H, s), 6.73 (2H, t, J=8Hz), 7.17 (1H, dd, J=2, 8Hz), 7.31 (1H, d, J=2Hz), 7.36 (2H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 7.64 (2H, d, J=8Hz)

Example 6

The following compounds were obtained according to a similar manner to that of Example 4.

(1) N-Benzyl-N-[3-(4-bromophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 172-174°C
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.43 (2H, s), 4.66 (2H, s), 6.73 (2H, t, J=8Hz), 6.98 (2H, m), 7.16-7.31 (7H, m), 7.42 (1H, d, J=8Hz), 7.61 (2H, d, J=8Hz)

(2) N-Benzyl-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 161-162°C
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.42 (2H, s), 4.66 (2H, s), 6.62 (1H, br s), 6.72 (2H, t, J=8Hz), 6.96-7.02 (2H, s), 7.16-7.47 (10H, m)

(3) N-Benzyl-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
NMR ($CDCl_3$, δ) : 2.18 (6H, s), 2.28 (3H, s), 2.47 (3H, s), 4.48 (2H, s), 4.75 (2H, s), 6.20 (1H, s), 6.88 (2H, s), 7.04-7.48 (12H, m)

(4) N-Benzyl-N-[3-(4-fluorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 149-150°C
NMR ($CDCl_3$, δ) : 2.43 (3H, s), 4.43 (2H, s), 4.65 (2H, s), 6.63 (1H, br s), 6.73 (2H, t, J=8Hz), 7.02 (2H, m), 7.14 (1H, d, J=8Hz), 7.26-7.43 (9H, m)

(5) N-Benzyl-N-[5-methyl-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea
mp : 158-159°C
NMR ($CDCl_3$, δ) : 2.44 (3H, s), 2.45 (3H, s), 4.41 (2H, s), 4.63 (2H, s), 6.66 (1H, br s), 6.72 (2H, t,

J = 8Hz), 6.98-7.43 (12H, m)

(6) N-Benzyl-N-[5-chloro-3-(4-methylphenyl)benzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 4.46 (2H, s), 4.70 (2H, s), 6.46 (1H, s), 6.74 (2H, t, J = 7Hz), 7.00-7.05 (2H, m), 7.20-7.53 (10H, m)

(7) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-methylbenzyl)-N'-(2,4,6-trifluorophenyl)-urea

mp : 166.5-167.5 °C

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.47 (3H, s), 4.40 (2H, s), 4.69 (2H, s), 6.58 (1H, s), 6.75 (2H, t, J = 7Hz), 6.90 (2H, d, J = 7Hz), 7.05 (2H, d, J = 7Hz), 7.18-7.49 (7H, m)

(8) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(2-phenylethyl)-N'-(2,4,6-trifluorophenyl)urea

mp : 159-161 °C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.77 (2H, t, J = 7Hz), 3.42 (2H, t, J = 7Hz), 4.57 (2H, s), 6.42 (1H, s), 6.73 (2H, t, J = 8Hz), 6.96 (2H, dd, J = 2, 8Hz), 7.17-7.30 (5H, m), 7.37 (2H, d, J = 8Hz), 7.40 (1H, d, J = 8Hz), 7.50 (2H, d, J = 8Hz)

(9) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(3,4-dichlorobenzyl)-N'-(2,4,6-trifluorophenyl)urea

mp : 193-195 °C

NMR ($CDCl_3$, δ) ; 2.45 (3H, s), 4.32 (2H, s), 4.60 (2H, s), 6.76 (2H, t, J = 8Hz), 6.82 (1H, d, J = 2Hz), 6.88 (1H, dd, J = 2, 8Hz), 7.19-7.32 (3H, m), 7.33 (2H, d, J = 8Hz), 7.42 (1H, d, J = 8Hz), 7.51 (2H, d, J = 8Hz)

(10) N-Benzyl-N-[(3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trichlorophenyl)urea

mp : 181-182 °C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.43 (2H, s), 4.69 (2H, s), 6.98-7.04 (3H, m), 7.17-7.48 (12H, m)

(11) N-Benzyl-N-(5-chloro-3-phenylbenzofuran-2-ylmethyl)-N'-(2,4,6-trifluorophenyl)urea

mp : 179-180 °C

NMR ($CDCl_3$, δ) : 4.43 (2H, s), 4.70 (2H, s), 6.48 (1H, s), 6.73 (2H, t, J = 7Hz), 6.94-7.01 (2H, m), 7.19-7.25 (3H, m), 7.30-7.54 (8H, m)

(12) N-(5-Chloro-3-phenylbenzofuran-2-ylmethyl)-N-cyclobutyl-N'-(2,4,6-trifluorophenyl)urea

mp : 142-143 °C

NMR ($CDCl_3$, δ) : 1.46-1.60 (2H, m), 1.87-2.08 (4H, m), 4.28 (1H, m), 4.83 (2H, s), 6.15 (1H, s), 6.72 (2H, t, J = 8Hz), 7.27-7.54 (8H, m)

(13) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclobutyl-N'-(2,4,6-trifluorophenyl)urea

mp : 111 °-112 °C

NMR ($CDCl_3$, δ) : 1.45-1.61 (2H, m), 1.88-2.11 (4H, m), 2.43 (3H, s), 4.27 (1H, m), 4.82 (2H, s), 6.25 (1H, S), 6.72 (2H, t, J = 8Hz), 7.16 (1H, dd, J = 2, 8Hz), 7.31 (1H, d, J = 2Hz), 7.41 (1H, d, J = 8Hz), 7.41-7.52 (4H, m)

(14) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclohexyl-N'-(2,4,6-trifluorophenyl)urea

mp : 170-173 °C

NMR ($CDCl_3$, δ) : 0.70-1.32 (6H, m), 1.58-1.67 (4H, m), 2.43 (3H, s), 4.02 (1H, m), 4.68 (2H, s), 6.74 (2H, t, J = 8Hz), 6.82 (1H, s), 7.18 (1H, dd, J = 2, 8Hz), 7.31 (1H, d, J = 2Hz), 7.42 (1H, d, J = 8Hz), 7.41 (2H, d, J = 8Hz), 7.52 (2H, d, J = 8Hz)

(15) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-cyclopentyl-N'-(2,4,6-trifluorophenyl)urea

mp : 151-152 °C

NMR ($CDCl_3$, δ) : 1.27-1.45 (6H, m), 1.73-1.83 (2H, m), 2.44 (3H, s), 4.43 (1H, m), 4.70 (2H, s), 6.74 (2H, t, J = 8Hz), 6.75 (1H, s), 7.18 (1H, dd, J = 2, 8Hz), 7.31 (1H, s), 7.41 (2H, d, J = 8Hz), 7.42 (1H, d, J = 8Hz), 7.51 (2H, d, J = 8Hz)

(16) N-[3-(4-Chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(2,4,6-trimethoxyphenyl)urea

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J = 7Hz), 1.18 (8H, br s), 1.45-1.55 (2H, m), 2.45 (3H, s), 3.27 (2H, t, J = 7Hz), 3.75 (6H, s), 3.80 (3H, s), 4.78 (2H, s), 5.89 (1H, s), 6.16 (2H, s), 7.12-7.19 (1H, m), 7.32-7.48 (6H, m)

(17) N-(5-Chloro-3-phenylbenzofuran-2-ylmethyl)-N-heptyl-N'-(2,4,6-trifluorophenyl)urea

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J = 7Hz), 1.15 (8H, br s), 1.43 (2H, m), 3.22 (2H, t, J = 7Hz), 4.78 (2H, s), 6.27 (1H, s), 6.72 (2H, t, J = 8Hz), 7.32 (1H, dd, J = 2, 8Hz), 7.43-7.53 (7H, m)

Example 7

To a solution of N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-methoxybenzyl)-N'-(2,4,6-trifluorophenyl)urea (701 mg) in methylene chloride (15 ml) was added boron tribromide (0.7 ml) dropwise at 0 °C and the mixture was stirred at the same temperature for 1 hours. The reaction mixture was poured into

ice cold water and washed with water, and dried. Evaporation of solvent followed by recrystallization from ethyl acetate-n-hexane gave N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-(4-hydroxybenzyl)-N'-(2,4,6-trifluorophenyl)urea (238 mg).
mp : 175-178 °C
NMR (CD_3OD, δ) : 2.43 (3H, s), 4.34 (2H, s), 4.72 (2H, s), 6.56-7.00 (6H, m), 7.12-7.58 (8H, m)

Example 8

A solution of N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(4-nitrophenyl)-urea (2.2 g) in methanol (30 ml) was hydrogenated over 10% palladium on carbon at 4 kg/cm2 pressure at ambient temperature for 7 hours. 10% Palladium on carbon was filtered off and washed with methanol. The combined filtrate and washing were concentrated under the reduced pressure to leave N-(4-aminophenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-heptylurea (2.0 g).
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.19 (8H, br s), 1.45 (2H, m), 2.43 (3H, s), 3.22 (2H, t, J=7Hz), 4.72 (2H, s), 6.30 (1H, s), 6.63 (2H, d, J=8Hz), 7.04 (2H, d, J=8Hz), 7.15 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=2Hz), 7.40 (1H, d, J=8Hz), 7.45 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz)

Example 9

A mixture of N-(4-aminophenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptylurea (0.3 g), acetic anhydride (0.3 ml) and pyridine (0.3 ml) was allowed to stand at ambient temperature overnight. The reaction mixture was poured into ice cold water and extracted with chloroform. The extract was washed with 3% hydrochloric acid and dilute aqueous sodium bicarbonate, and dried. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with chloroform gave N-(4-acetylaminophenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-heptylurea (0.28 g).
NMR ($CDCl_3$, δ) : 0.84 (3H, t, J=7Hz), 1.15 (8H, br s), 1.43 (2H, m), 2.04 (3H, s), 2.42 (3H, s), 3.22 (2H, t, J=7Hz), 4.72 (2H, s), 6.72 (1H, s), 7.01-7.28 (6H, m), 7.37 (1H, d, J=8Hz), 7.42 (2H, d, J=8Hz), 7.46 (2H, d, J=8Hz), 8.20 (1H, s)

Example 10

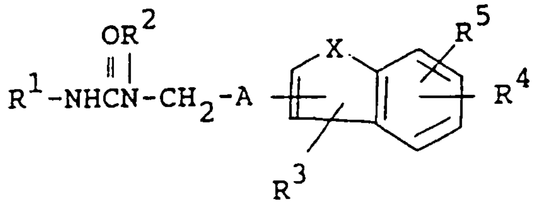
A mixture of N-(4-aminophenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-heptylurea (315 mg), methanesulfonyl chloride (90 mg) and pyridine (0.5 ml) was allowed to stand at ambient temperature overnight. The reaction mixture was poured into ice cold water and extracted with chloroform. The extract was washed with dilute hydrochloric acid and dilute aqueous sodium bicarbonate, and dried. Evaporation of solvent gave a residue which was chromatographed on silica gel. Elution with chloroform gave N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N-heptyl-N'-(4-methylsulfonylaminophenyl)urea (0.15 g).
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.16 (8H, br s), 1.45 (2H, m), 2.43 (3H, s), 2.90 (3H, s), 3.23 (2H, t, J=7Hz), 4.73 (2H, s), 6.65 (1H, s), 7.02-7.22 (5H, m), 7.29 (1H, d, J=2Hz), 7.39 (1H, d, J=8Hz), 7.43 (2H, d, J=8Hz), 7.49 (2H, d, J=8Hz)

Example 11

A mixture of N-(4-aminophenyl)-N'-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-heptylurea (0.8 g), 37% formaldehyde (0.3 g) and 10% palladium on carbon (0.13 g) in methanol (20 ml) was hydrogenated at ambient temperature at 4 kg/cm2 pressure for 20 hours. 10% Palladium on carbon was filtered off and washed with methanol. The combined filtrate and washings were concentrated under the reduced pressure to leave a residue which was chromatographed on silica gel. Elution with chloroform gave N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(4-dimethylaminophenyl)-N-heptylurea (0.5 g).
NMR ($CDCl_3$, δ) : 0.86 (3H, t, J=7Hz), 1.18 (8H, br s), 1.46 (2H, m), 2.43 (3H, s), 2.39 (6H, s), 3.22 (2H, t, J=7Hz), 4.73 (2H, s), 6.32 (1H, s), 6.70 (2H, d, J=8Hz), 7.13 (2H, d, J=8Hz), 7.15 (1H, dd, J=2, 8Hz), 7.30 (1H, d, J=2Hz), 7.40 (1H, d, J=8Hz), 7.46 (4H, s)

Claims

1. A compound of the formula :



(I)

wherein

R¹ is aryl which may be substituted with halogen, nitro, amino, lower alkylamino, lower alkoxy or acylamino,

R² is hydrogen; alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, cyclo(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy;

R³ is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,

R⁴ is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,

R⁵ is hydrogen, halogen, lower alkyl or aryl,

A is a single bond or lower alkylene, and

X is O, S or NH,

provided that

R³ is aryl which may be substituted with halogen, nitro, amino or lower alkyamino, or

R⁴ is halogen, lower alkoxy or aryl which may be substituted with halogen,

when

R² is cycloalkyl,

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1,
wherein

R² is hydrogen; alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy.

3. A compound according to claim 2,
wherein

R¹ is aryl which may be substituted with halogen, nitro, amino, lower alkyamino or lower alkoxy,

R² is alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy, and

R⁵ is hydrogen.

4. A compound according to claim 3,
wherein

R² is alkyl; cycloalkyl; or lower alkyl which is substituted with aryl.

5. A compound according to claim 3,
wherein

R¹ is aryl which may be substituted with halogen or lower alkoxy, and

X is O or S.

6. A compound according to claim 5,
wherein

R³ is hydrogen or aryl which may be substituted with halogen, and

R⁴ is hydrogen, halogen, lower alkyl or aryl which may be substituted with halogen.

7. A compound according to claim 6,
wherein

R^2 is alkyl; cycloalkyl; or lower alkyl which is substituted with aryl.

8. A compound according to claim 6,
wherein

- R^1 is phenyl which is substituted with 1 to 3 lower alkyl, halogen or lower alkoxy substituent(s).
- R^2 is alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, furyl, thienyl, pyridyl or phenyl optionally substituted with substituent(s) sleceted from the group consisting of lower alkyl, halogen, hydroxy and lower alkoxy; and
- R^3 is phenyl which may be substituted with lower alkyl or halogen; or
- R^1 and R^2 are each defined above, and
- R^4 is halogen or phenyl which may be substituted with lower alkyl or halogen.

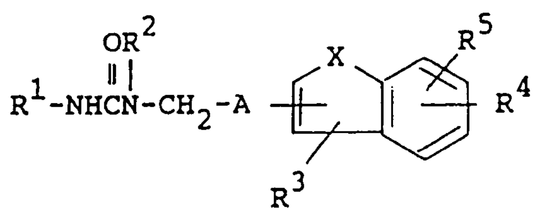
9. A compound according to claim 8,
wherein

- R^1 is phenyl substituted with 1 to 3 halogen,
- R^2 is lower alkyl which may be substituted with furyl, thienyl or phenyl optionally substituted with substituent(s) selected from the group consisting of lower alkyl and halogen,
- R^3 is phenyl substituted with lower alkyl or halogen, and
- R^4 is halogen or lower alkyl.

10. N-Benzyl-N-[3-(4-chlorophenyl)-5-methylbenzofuran-2-ylmethyl]-N'-(2,4,6-trifluorophenyl)urea.

11. N-[3-(4-Bromophenyl)-5-methylbenzofuran-2-ylmethyl]-N-furfuryl-N'-(2,4,6-trifluorophenyl)urea.

12. A process for preparing a compound of the formula:



(I)

wherein

- R^1 is aryl which may be substituted with halogen, nitro, amino, lower alkylamino, lower alkoxy or acylamino,
- R^2 is hydrogen; alkyl; cycloalkyl; or lower alkyl which is substituted with cyclo(lower)alkyl, cyclo(lower)alkenyl, a heterocyclic group or aryl optionally substituted with substituent(s) selected from the group consisting of halogen, hydroxy and lower alkoxy;
- R^3 is hydrogen, lower alkyl or aryl which may be substituted with halogen, nitro, amino or lower alkylamino,
- R^4 is hydrogen, halogen, lower alkyl, lower alkoxy or aryl which may be substituted with halogen,
- R^5 is hydrogen, halogen, lower alkyl or aryl,
- A is a single bond or lower alkylene, and
- X is O, S or NH,

provided that

- R^3 is aryl which may be substituted with halogen, nitro, amino or lower alkylamino, or
- R^4 is halogen, lower alkoxy or aryl which may be substituted with halogen,

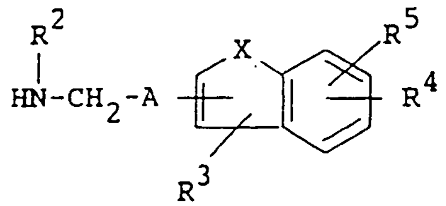
when

- R^2 is cycloalkyl,

or pharmaceutically acceptable salts therof, which comprises,
(a) reacting a compound of the formula :

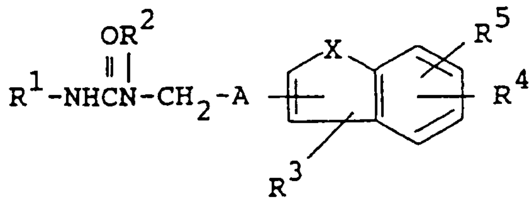
R^1-NCO (II)

with a compound of the formula :



(III)

or its salt to provide a compound of the formula :

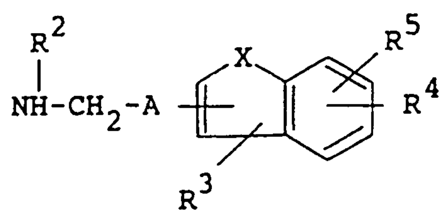


(I)

or its salt, in the above formulas, R^1, R^2, R^3, R^4, R^5, A and X are each as defined above, or
(b) subjecting a compound of the formula :

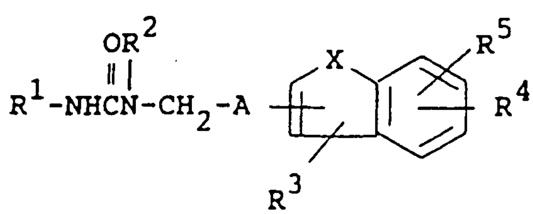
R^1-NH_2 (IV)

or its salt and a compound of the formula :



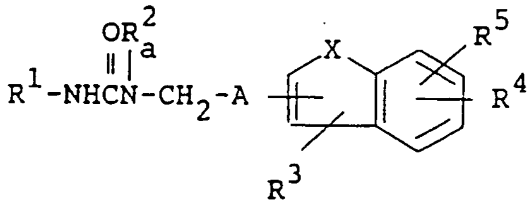
(III)

or its salt to formation reaction of ureido group to provide a compound of the formula :



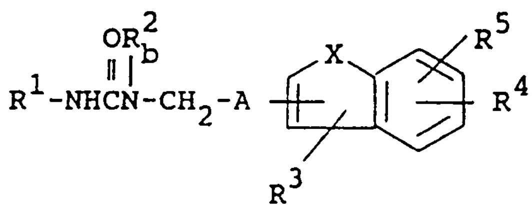
(I)

or its salt, in the above formulas, R^1 R^2 R^3 R^4 R^5 A and X are each as defined above, or
(c) subjecting a compound of the formula :



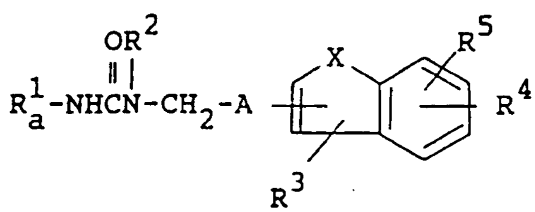
(Ia)

or its salt to dealkylation reaction to provide a compound of the formula :



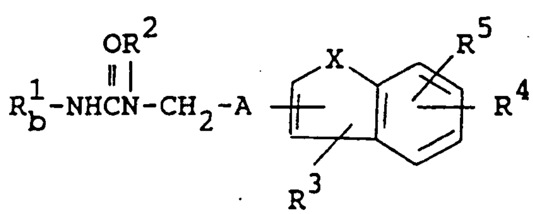
(Ib)

or its salt, in the above formulas,
R^1, R^3, R^4, R^5, A and X are each as defined above,
R^2_a is lower alkyl which is substituted with aryl substituted with alkoxy, and
R^2_b is lower alkyl which is substituted with aryl substituted with hydroxy, or
(d) subjecting a compound of the formula :



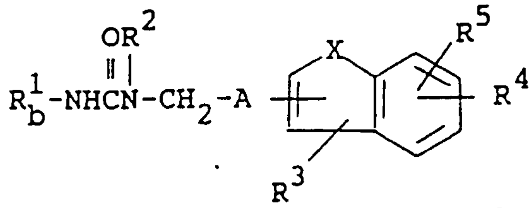
(Ic)

or its salt to reduction
to provide a compound of the formula :



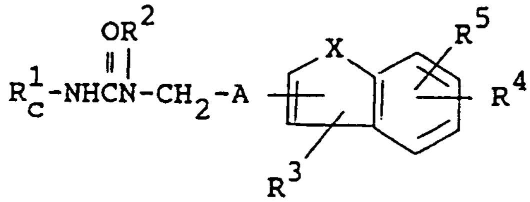
(Id)

or its salt, in the above formulas,
R^2, R^3, R^4, R^5, A and X are each as defined above,
R^1_a is aryl substituted with nitro, and
R^1_b is aryl substituted with amino, or
(e) reacting a compound of the formula :



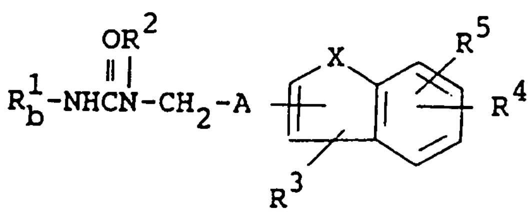
(Id)

or its salt with an acylating agent to provide a compound of the formula :



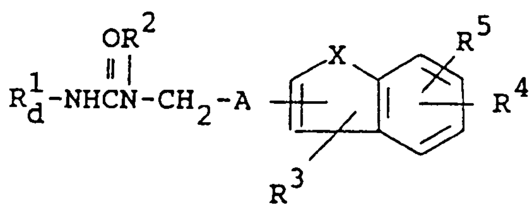
(Ie)

or its salt, in the above formulas,
R_b^1, R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_c^1 is aryl substituted with acylamino, or
(f) reacting a compound of the formula :



(Id)

or its salt with an alkylating agent to provide a compound of the formula :



(If)

or its salt, in the above formulas,
R_b^1, R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_d^1 is aryl substituted with lower alkylamino.

13. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

14. A compound of claim 1 for use as a medicament.

15. A compound of claim 1 for use in therapeutic treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

16. Use of a compound of claim 1 for the manufacture of a medicament for treating hypercholesterolemia,

hyperlipidemia, atherosclerosis or diseases caused thereby.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 7863

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 399 422 (TAKEDA CHEMICAL INDUSTRIES LTD.) * page 3, line 5 - page 4, line 4 * * page 4, line 55 - page 5, line 45; claims 1,14,16 * ---	1,12-16	C07D333/58 C07D307/81 C07D209/14 C07D407/12 C07D405/12 C07D409/12 A61K31/44 A61K31/40 A61K31/38 A61K31/335
D,A	US-A-4 623 662 (V. G. DE VRIES) * column 1, line 1 - column 4, line 19 * * column 6, line 27 - column 7, line 18; claim 1 * ---	1,12-16	
D,P,A	WO-A-9 113 871 (YAMANOUCHI PHARMACEUTICAL CO., LTD.) * abstract; examples * -----	1,12-16	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	07 AUGUST 1992	B. Paisdor

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)